Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for treating acute high altitude illness (Review)

Simancas-Racines D, Arevalo-Rodriguez I, Osorio D, Franco JVA, Xu Y, Hidalgo R

Simancas-Racines D, Arevalo-Rodriguez I, Osorio D, Franco JVA, Xu Y, Hidalgo R.
Interventions for treating acute high altitude illness.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD009567.
DOI: 10.1002/14651858.CD009567.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for treating acute high altitude illness

Daniel Simancas-Racines[1], Ingrid Arevalo-Rodriguez[1,2,3], Dimelza Osorio[1], Juan VA Franco[4], Yihan Xu[5], Ricardo Hidalgo[1]

[1]Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador. [2]Clinical Biostatistics Unit, Hospital Universitario Ramon y Cajal (IRYCIS), Madrid, Spain. [3]CIBER Epidemiology and Public Health (CIBERESP), Madrid, Spain. [4]Argentine Cochrane Centre, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina. [5]Wee Kim Wee School of Communication and Information, Nanyang Technological University, Singapore City, Singapore

Contact address: Daniel Simancas-Racines, Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador. danielsimancas10@gmail.com, dsimancas@ute.edu.ec.

Editorial group: Cochrane Emergency and Critical Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2018.

Citation: Simancas-Racines D, Arevalo-Rodriguez I, Osorio D, Franco JVA, Xu Y, Hidalgo R. Interventions for treating acute high altitude illness. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD009567. DOI: 10.1002/14651858.CD009567.pub2.

ABSTRACT

Background

Acute high altitude illness is defined as a group of cerebral and pulmonary syndromes that can occur during travel to high altitudes. It is more common above 2500 metres, but can be seen at lower elevations, especially in susceptible people. Acute high altitude illness includes a wide spectrum of syndromes defined under the terms 'acute mountain sickness' (AMS), 'high altitude cerebral oedema' and 'high altitude pulmonary oedema'. There are several interventions available to treat this condition, both pharmacological and non-pharmacological; however, there is a great uncertainty regarding their benefits and harms.

Objectives

To assess the clinical effectiveness, and safety of interventions (non-pharmacological and pharmacological), as monotherapy or in any combination, for treating acute high altitude illness.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS, ISI Web of Science, CINAHL, Wanfang database and the World Health Organization International Clinical Trials Registry Platform for ongoing studies on 10 August 2017. We did not apply any language restriction.

Selection criteria

We included randomized controlled trials evaluating the effects of pharmacological and non-pharmacological interventions for individuals suffering from acute high altitude illness: acute mountain sickness, high altitude pulmonary oedema or high altitude cerebral oedema.

Data collection and analysis

Two review authors independently assessed the eligibility of study reports, the risk of bias for each and performed the data extraction. We resolved disagreements through discussion with a third author. We assessed the quality of evidence with GRADE.

Main results

We included 13 studies enrolling a total of 468 participants. We identified two ongoing studies. All studies included adults, and two studies included both teenagers and adults. The 13 studies took place in high altitude areas, mostly in the European Alps. Twelve studies included participants with acute mountain sickness, and one study included participants with high altitude pulmonary oedema. Follow-up was

usually less than one day. We downgraded the quality of the evidence in most cases due to risk of bias and imprecision. We report results for the main comparisons as follows.

Non-pharmacological interventions (3 studies, 124 participants)

All-cause mortality and complete relief of AMS symptoms were not reported in the three included trials. One study in 64 participants found that a simulated descent of 193 millibars versus 20 millibars may reduce the average of symptoms to 2.5 vs 3.1 units after 12 hours of treatment (clinical score ranged from 0 to 11 – worse; reduction of 0.6 points on average with the intervention; low quality of evidence). In addition, no complications were found with use of hyperbaric chambers versus supplementary oxygen (one study; 29 participants; low-quality evidence).

Pharmacological interventions (11 trials, 375 participants)

All-cause mortality was not reported in the 11 included trials. One trial found a greater proportion of participants with complete relief of AMS symptoms after 12 and 16 hours when dexamethasone was administered in comparison with placebo (47.1% versus 0%, respectively; one study; 35 participants; low quality of evidence). Likewise, when acetazolamide was compared with placebo, the effects on symptom severity was uncertain (standardized mean difference (SMD) −1.15, 95% CI −2.56 to 0.27; 2 studies, 25 participants; low-quality evidence). One trial of dexamethasone in comparison with placebo in 35 participants found a reduction in symptom severity (difference on change in the AMS score: 3.7 units reported by authors; moderate quality of evidence). The effects from two additional trials comparing gabapentin with placebo and magnesium with placebo on symptom severity at the end of treatment were uncertain. For gabapentin versus placebo: mean visual analogue scale (VAS) score of 2.92 versus 4.75, respectively; 24 participants; low quality of evidence. For magnesium versus placebo: mean scores of 9 and 10.3 units, respectively; 25 participants; low quality of evidence). The trials did not find adverse events from either treatment (low quality of evidence). One trial comparing magnesium sulphate versus placebo found that flushing was a frequent event in the magnesium sulphate arm (percentage of flushing: 75% versus 7.7%, respectively; one study; 25 participants; low quality of evidence).

Authors' conclusions

There is limited available evidence to determine the effects of non-pharmacological and pharmacological interventions in treating acute high altitude illness. Low-quality evidence suggests that dexamethasone and acetazolamide might reduce AMS score compared to placebo. However, the clinical benefits and harms related to these potential interventions remain unclear. Overall, the evidence is of limited practical significance in the clinical field. High-quality research in this field is needed, since most trials were poorly conducted and reported.

PLAIN LANGUAGE SUMMARY

Treatments for high altitude (mountain) illness

Background

Acute high altitude illness, also known as acute mountain sickness, may present with a variety of symptoms. It is caused by the decreasing level of oxygen at increasingly high altitudes; and it can be experienced when reaching a high altitude when travelling, hiking or climbing mountains or other elevated areas. People going to altitudes over 4000 metres, females, people younger than mid-adulthood , and people with a history of migraine are at greater risk of suffering from altitude sickness. The most common symptoms are headache, loss of appetite , insomnia, and nausea. However, severe forms can include confusion, difficulty walking, progressive cough, shortness of breath, and even death.

Review question

What are the benefits and risks of different treatments for people suffering from high altitude illness?

Study characteristics

We included 13 studies with a total of 468 participants. Most studies included participants with mild or moderate forms of mountain sickness, and only one study included the severe neurological (disorder of the nervous system) form. Follow-up was usually less than one day. We also identified two ongoing studies.

Key results

We found studies evaluating the following interventions: simulated descent with a hyperbaric chamber (medical use of oxygen in a special chamber at greater than atmospheric pressure to increase the availability of oxygen in the body); oxygen; medicines: acetazolamide, dexamethasone, ibuprofen, paracetamol, gabapentin, sumatriptan, nitric oxide, and magnesium sulphate. None of the studies reported the effects of these interventions on all-cause mortality. The report of complete relief from acute mountain sickness symptoms, and adverse events was infrequent. Studies related to simulated descent with the use of a hyperbaric chamber did not find additional benefits or harms related to this intervention (3 studies, 124 participants). In addition, studies related to administration of medicines found some

benefits in terms of reduction of symptoms with the use of acetazolamide (2 studies, 25 participants), and dexamethasone (1 study, 35 participants), without an increase in side effects.

Quality of the evidence

The quality of the evidence we found was low, and thus our certainty in the findings is limited. There was insufficient information on how the studies were conducted, and in some cases there was evidence of tampering at some stages of the trials. Furthermore, the number of persons in each study was very small (< 30 participants), and therefore the results were not clear (imprecise). Some studies were not blinded (that is, participants knew what experimental treatment they were receiving), and this could have affected how the participants evaluated their own symptoms.

Summary of findings for the main comparison. Non-pharmacological interventions for treating acute high altitude illness

Non-pharmacological interventions for treating acute high altitude illness

Patient or population: people suffering from high altitude illness
Setting: Swiss–Italian border, USA.
Intervention: hyperbaric chamber, simulated descent (193 millibars)
Comparison: supplementary oxygen, simulated descent (20 millibars)

Outcomes and intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with various interventions	Risk with non-pharmacological interventions				
All-cause mortality	-	-	-	-	-	Not reported
Complete relief of AMS symptoms	-	-	-	-	-	Not reported
Reduction in symptom score severity at 12 hours (Clinical score: ranged from 0 to 11 (worse)) **Intervention:** Simulated descent of 193 millibars versus 20 millibars	The mean score in the control group was 3.1	The mean score in the intervention group was 2.5	0.6 points lower with intervention	64 (1 RCT)	⊕⊕## **Low** [1]	
Adverse effects during treatment **Intervention:** Hyperbaric chamber/ 160 millibars versus supplementary oxygen	0 per 1000	0 per 1000	Nil	29 (1 RCT)	⊕⊕## **Low**[1]	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Quality of evidence downgraded by two levels due to serious risk of bias (performance bias (blinding was not specified), attrition bias and selective reporting bias) and serious imprecision (optimal information size criteria not achieved)

Summary of findings 2. Pharmacological interventions for treating acute high altitude illness

Pharmacological interventions for treating acute high altitude illness

Patient or population: people suffering from high altitude illness
Setting: Alaska, borders between China, India and Pakistan, Iran, Nepal, Tibet, Swiss–Italian border.
Intervention: pharmacological interventions (dexamethasone, acetazolamide, gabapentin)
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with various interventions	Risk with pharmacological interventions				
All-cause mortality		-	-	-	-	-	Not reported
Complete relief of AMS symptoms (12 to 16 hours after treatment) **Scale used**: Acute Mountain Sickness score (ranged from 0 to 9 (worse))	Dexamethasone versus placebo	0 per 1000	471 per 1000	No estimable	35 (1 RCT)	⊕⊕## **Low** [1]	
Reduction in symptom score severity **Time of measurement**: 1 to 48 hours after treatment, end of treatment **Scale of measurement:** Self-administered AMS questionnaires (ranged from 0 to 90 (worse)), AMS Symptom Questionnaire (ranged from 0 to 22 (worse)), Acute Mountain Sickness score (ranged from 0 to 9	Acetazolamide versus placebo			**Standardized Mean Difference** 1.15 lower (2.56 lower to 0.27 higher)	25 (2 RCTs)	⊕⊕## **Low** [2]	
	Dexamethasone versus placebo	Mean change from baseline: 0.4 units	Mean change from baseline: 4.1 units	Difference of 3.7 units (re-	35 (1 RCT)	⊕⊕⊕# **Moderate** [3]	

(worse)), HAH Visual analogue score (VAS) (range no stated), Lake Louise Score (from 0 to 15 (worse)),				ported by trial authors)		
	Gabapentin versus placebo	Mean VAS score: 4.75	Mean VAS score: 2.92	Not stated	24 (1 RCT)	⊕⊕## **Low** [4]
	Magnesium versus placebo	Mean score: 10.3 units	Mean score: 9 units	Not stated	25 (1 RCT)	⊕⊕## **Low** [4]
Adverse effects **Time of measurement**: 1 to 48 hours after treatment, end of treatment **Scale of measurement**:**n**ot stated	Acetazolamide versus placebo	No reported	0 per 1000	Not estimable	25 (1 RCT)	⊕⊕## **Low** [4]
	Gabapentin versus placebo	0 per 1000	0 per 1000	Not stated	24 (1 RCT)	⊕⊕## **Low** [4]
	Magnesium sulphate versus placebo	77 per 1000	750 per 1000	Not stated	25 (1 RCT)	⊕⊕## **Low** [4]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR**: Risk ratio; **OR**: Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Quality of evidence downgraded by two levels due to very serious risk of bias (multiple unclear biases and high risk of selective reporting bias)
[2] Quality of evidence downgraded by two levels due to serious risk of bias (selection bias) and serious inconsistency (I^2 = 58%).
[3] Quality of evidence downgraded by one level due to serious risk of bias (selection, performance and detection bias).
[4] Quality of evidence downgraded by two levels due to serious risk of bias and serious imprecision.

BACKGROUND

High altitude is arbitrarily classified as high (1500 to 3500 metres), very high (3500 to 5500 metres), and extreme (above 5500 metres) (Paralikar 2010). At high altitude there is a drop in barometric pressure, which causes a decrease in the partial pressure of oxygen. In most cases, this hypobaric hypoxia triggers physiological responses that help the individual tolerate and adapt to the low oxygen conditions. However in other cases there are abnormal responses, that in turn cause one of three forms of acute altitude illness: acute mountain sickness (AMS), high altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE) (Luks 2017).

Acute high altitude illness is more common above 2500 metres, but can be seen at lower elevations, especially in susceptible people. Factors such as the rate of ascent, the absolute change in altitude and individual physiology are the primary determinants as to whether HAI will develop or not (Palmer 2010). People going to altitudes over 4000 metres, females, people younger than mid-adulthood, and people with a history of migraine are at greater risk of suffering from altitude sickness (Bärtsch 2013; Canoui-Poitrine 2014).

Description of the condition

High altitude illness (HAI)

The potential medical problems associated with a high altitude excursion are many, and terminology has sometimes confused their classification. For the purposes of this review, high altitude illness (HAI) is defined as a group of cerebral and pulmonary syndromes that can occur during travel to elevations above 2500 metres (Luks 2014). This includes syndromes covered by the terms 'acute mountain sickness' (AMS), 'high altitude cerebral oedema' (HACE),and 'high altitude pulmonary oedema' (HAPE). The risk categories for acute mountain sickness are shown in Appendix 1 (Luks 2010; Luks 2014). HAI is considered as an important cause of mountain mortality (Windsor 2009).

Other medical problems that may be encountered at high altitudes include acute hypoxia, cerebrovascular syndromes, peripheral oedema, retinopathy, retinal haemorrhage, thromboembolism, sleep disorders and periodic breathing, high altitude pharyngitis and bronchitis, ultraviolet exposure and keratitis (snow blindness) and exacerbation of pre-existing illness (CATMAT 2007; Palmer 2010; Schoene 2008); however these will not be considered in this review.

Acute mountain sickness (AMS) and high altitude cerebral oedema (HACE)

AMS is a neurological disorder characterized by headache, anorexia, nausea and sometimes vomiting, light-headedness, insomnia, and fatigue or loss of energy (Palmer 2010). Headache is the most prevalent symptom (Luks 2017). In contrast, HACE is a potentially fatal neurologic disorder that is characterized by altered consciousness or ataxia (Imray 2010), or both. If left untreated, HACE can result in death subsequent to brain herniation (Bailey 2009). HACE is widely viewed as the end stage of AMS, and is normally preceded by symptoms of AMS (Basnyat 2003), which suggests that they result from a similar pathophysiologic process (Palmer 2010). Both syndromes are characterized by oedematous brain swelling, and intracranial hypertension (Luks 2017). The severity of AMS can be graded using the Lake Louise Questionnaire, Environmental Symptoms Questionnaire, or by the use of a simple analogue scale (Imray 2010).

The pathophysiology apparently involves an interaction of multiple physiological responses to hypoxia (ventilation, cerebral vasculature, autonomic nervous system and nociceptive thresholds), and anatomical factors such as the compensatory capacity for cerebrospinal fluid, and the capacity of venous outflow (Luks 2017).

High altitude pulmonary oedema (HAPE)

HAPE is a non-cardiogenic pulmonary oedema (Smedley 2013). It is characterized by cough, progressive dyspnoea with exertion, and decreased exercise tolerance, generally developing within two to four days after arrival at high altitude (Hall 2011). HAPE is rare after one week of acclimatization at a particular altitude (Maggiorini 2010; Palmer 2010). Hypoxia is the trigger that results in a complex cascade of events leading to HAPE (Stream 2008). Essentially, HAPE is due to a "persistent imbalance between the forces that drive water into the airspace and the biologic mechanisms for its removal" (Scherrer 2010). The hallmark of this condition is hypoxic pulmonary hypertension, which may be mediated via at least three potential mechanisms: defective pulmonary nitric oxide synthesis; exaggerated endothelin-1 synthesis; and exaggerated sympathetic activation (Scherrer 2010). A defect in alveolar transepithelial sodium transport has also been suggested (Scherrer 2010). An extensive review of pulmonary hypertension induced by high altitude is reported by Pasha 2010.

Epidemiology of acute high altitude illness (HAI)

It has been estimated that 25% of people at moderate altitude are affected by acute mountain sickness (AMS), and 50% to 85% of travellers at 4000 meters or more (Eide 2012). The incidence of high altitude cerebral oedema and high altitude pulmonary oedema is much lower than for AMS, with estimates in the range of 0.1% to 4.0% (Luks 2010). Rapid ascent, poor acclimatization, physical exertion at altitude, young age, and history of prior altitude illness are major risk factors to develop HAI (Eide 2012). Other risk factors are permanent residence lower than 900 metres; obesity (Ri-Li 2003); and coronary heart disease (Dehnert 2010).

(See Appendix 2 for a glossary of medical terms.)

Description of the intervention

Interventions for treating HAI can be broadly classified as pharmacological and non-pharmacological. Several consensus statements and guidelines have been published in this area. Some of them have been published by the Wilderness Medical Society (Luks 2014); the Committee to Advise on Tropical Medicine and Travel statement (CATMAT 2007); and the Centers for Disease Control and Prevention (CDC; CDC Yellow Book 2016).

A) Non-pharmacological interventions

1. Descent (Hackett 2004)
2. Hyperbaric chamber (Bärtsch 1993; Kasic 1991; Keller 1995)
3. Portable pressure bag or Gamow bag (Austin 1998; Freeman 2004; Zafren 1998)
4. Breathing system designed to conserve oxygen supplies at high altitude (Pattinson 2005)

5. Positive airway pressure and other therapies (Koch 2009; Schoene 1985)

B) Pharmacological interventions

1. Oxygen (Hill 1909; Zafren 1996)
2. Carbonic anhydrase inhibitors: acetazolamide (Grissom 1992)
3. Glucocorticosteroids: dexamethasone (Ferrazzini 1987; Hackett 1988; Hackett 2004; Levine 1989; Wright 2008); medroxyprogesterone (Wright 2008)
4. Non-steroidal anti-inflammatory drugs (NSAIDs): ibuprofen (Broome 1994; Harris 2003); paracetamol (Harris 2003); and aspirin (Burtscher 2001)
5. Selective 5-hydroxytryptamine (1) receptor agonist: sumatriptan (Utiger 2002)
6. Inhaled nitric oxide (Scherrer 1996; Schoene 2004)
7. Anticonvulsant drugs: gabapentin (Jafarian 2007a)
8. Diuretics: furosemide (Hultgren 1975)
9. Calcium channel blockers: nifedipine (Oelz 1989; Oelz 1992)
10. Non-selective phosphodiesterase inhibitor (theophylline or aminophylline) (Fisher 2000)
11. Magnesium (Dumont 2004)

How the intervention might work

Both pharmacological and non-pharmacological interventions are used to treat acute high altitude illness; however, immediate descent or evacuation to a lower altitude is lifesaving and the treatment of choice for patients with fully developed severe high altitude illness (Luks 2014). Treatments other than descent are considered when descent is not possible due to bad weather, terrain or other logistical factors.

Some of the ways the pharmacological and non-pharmacological treatments might work are as follows.

A) Acute mountain sickness (AMS) and high altitude cerebral oedema (HACE)

1. Carbonic anhydrase inhibitors (acetazolamide, methazolamide) inhibit carbonic anhydrase in the kidneys, resulting in bicarbonaturia and metabolic acidosis. This results in hyperventilation in order to compensate through a respiratory alkalosis and thus this drug causes improvements in ventilation in order to respond more fully to hypoxic stimuli at altitude (Leaf 2007). Acetazolamide can also cause pulmonary vasodilation unrelated to carbonic anhydrase inhibition (Höhne 2007).
2. Steroids (dexamethasone and medroxyprogesterone): dexamethasone blocks hypoxia-induced endothelial dysfunction (Murata 2004; Murata 2005); and medroxyprogesterone acts as a respiratory stimulant (Wright 2004).
3. Furosemide: this diuretic drug would reduce pulmonary extravascular fluid accumulation; however, diuretics have no role in high altitude pulmonary oedema (HAPE) treatment particularly because many HAPE patients have concurrent intravascular volume depletion (Luks 2010).
4. Non-steroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, paracetamol, aspirin): a prostaglandin-mediated increase in cerebral microvascular permeability may contribute to the pathophysiology of AMS, and treatment with prostaglandin synthetase inhibitors may reduce this response (CATMAT 2007).
5. Selective 5-hydroxytryptamine (1) receptor agonists (sumatriptan) are selective cerebral vasoconstrictors (Jafarian 2007b).
6. Anticonvulsant drugs (gabapentin): gabapentin is an anticonvulsant drug with analgesic properties (Cheng 2006; Maneuf 2006).
7. Hyperbaric therapy (chambers, manual air pump, fabric pressure bags or Gamow bags) simulate descent and gives symptomatic improvement within a few hours as a temporary measure while awaiting descent (CATMAT 2007).

B) High altitude pulmonary oedema (HAPE)

1. Calcium channel blockers (e.g. nifedipine) reduce pulmonary vascular resistance (Hackett 1992).
2. Nitric oxide is an endothelium-derived relaxing factor which attenuates the pulmonary vasoconstriction produced by hypoxia (Blitzer 1996; Scherrer 1996; Schoene 2004; Wang 2003).
3. Non-selective phosphodiesterase inhibitor (theophylline or aminophylline): the antihypoxia and antioxidation effects of aminophylline may reduce periodic breathing, cerebral and pulmonary microvascular permeability (Yang 2007), and also pulmonary artery pressure (Wright 2008).
4. Positive airway pressure and other therapies: breathing against a positive expiratory pressure improves arterial oxygen saturation (Bärtsch 1992; Larson 1992; Schoene 1985).

(See Appendix 3 for reported adverse effects of the pharmacological interventions).

Why it is important to do this review

It is important to conduct this systematic review for a number of reasons. First, many people travel to recreational areas located at high altitude, and with rapidly increasing levels of world travel, this trend is increasing (CATMAT 2007). Second, there is considerable uncertainty about the true effectiveness of the many approaches to treating acute HAI (Adams 2004; Bärtsch 2004; CATMAT 2007; Elphick 2004), and their clinical effectiveness and safety must be assessed. This is especially important, considering that travellers may be falsely reassured that they will be safe going to high altitudes, as they believe they have an effective remedy in their rucksacks in case they get ill.

A systematic review, including a rigorous assessment of the risk of bias, of the most up-to-date evidence will help clinicians make informed decisions on the use of non-pharmacological and pharmacological interventions for treating acute HAI.

OBJECTIVES

To assess the clinical effectiveness, and safety of interventions (non-pharmacological and pharmacological), as monotherapy or in any combination, for treating acute high altitude illness.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) irrespective of publication status (trials may be unpublished or published as an article, an abstract or a letter). We applied no language and no country limitation. We did not apply restrictions with respect to periods of follow-up. We excluded studies about chronic mountain sickness or Monge's syndrome (Leissner 2009; León-Velarde 2010; Monge 1942). We excluded quasi-randomized studies, and prospective observational studies for evaluating clinical effectiveness.

Types of participants

We included trials involving people with high altitude Illness (acute mountain sickness/high altitude cerebral oedema, or high altitude pulmonary oedema, or both), with or without a history of high altitude Illness. We did not apply any restriction by age and gender.

Types of interventions

Interventions

A) Non-pharmacological interventions

1. Descent
2. Hyperbaric chamber
3. Portable pressure bag or Gamow bag
4. Breathing system designed to conserve oxygen supplies at high altitude
5. Positive airway pressure

B) Pharmacological interventions

1. Oxygen
2. Carbonic anhydrase inhibitors (e.g. acetazolamide)
3. Glucocorticosteroids: dexamethasone and medroxyprogesterone
4. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol: ibuprofen, aspirin and paracetamol
5. Selective 5-hydroxytryptamine (1) receptor agonist: sumatriptan
6. Inhaled nitric oxide
7. Anticonvulsant drugs (e.g. gabapentin)
8. Diuretics (e.g. furosemide)
9. Calcium channel blockers: nifedipine
10. Magnesium

Comparisons

Placebo, monotherapy or any combination (non-pharmacological plus pharmacological; pharmacological interventions).

Types of outcome measures

Primary outcomes

1. All-cause mortality: we assessed this outcome through three approaches.
   a. The number of deaths from any cause divided by the number of the participants in each group.
   b. To determine how many deaths were caused by HAPE or HACE: the number of deaths from high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE) divided by the number of participants in each group.
   c. To determine how lethal HAPE or HACE were: the number of deaths by HAPE or HACE divided by the number of participants affected by HAPE or HACE in each group.
2. Complete relief of acute mountain sickness symptoms: defined as the complete absence of acute mountain sickness symptoms by the end of the study.

Secondary outcomes

1. Reduction in illness severity scores of acute mountain syndrome (headache, nausea, insomnia and dizziness; alone or in any combination) evaluated by the Lake Louise Questionnaire (Roach 1993), Environmental Symptoms Questionnaire (Sampson 1983), or any other validated scale. Because these different scales are not directly comparable, we analysed the results for each scale separately.
2. Adverse events
   a. Adverse events: total adverse events and total serious adverse events. We defined adverse events as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (Nebeker 2004). Adverse drug reaction was defined as "a response to a drug which is noxious and uninitiated, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic functions" (Nebeker 2004).

(See Appendix 3 for commonly described adverse events of the pharmacological approaches).

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies specifically designed to identify relevant trials without restrictions to language or publication status.

We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7)
2. MEDLINE (Ovid SP, 1966 to 10 August 2017)
3. Embase (www.embase.com, 1988 to 10 August 2017)
4. LILACS (BIREME interface, 1982 to 10 August 2017)
5. ISI Web of Science (1973 to 10 August 2017)
6. CINAHL (EBSCO host, 1982 to 10 August 2017)
7. Wanfang (Wanfangdata.com to 10 August 2017)

We developed a subject-specific search strategy in MEDLINE, and used that as the basis for the search strategies in the other databases listed. Where appropriate, the search strategy was expanded with search terms for identifying RCTs. Our search strategies can be found in Appendix 4.

Searching other resources

We scanned the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch) for ongoing and unpublished trials on 19 August 2017; (see Appendix 5).

We developed the search strategy in consultation with the Information Specialist.

We scanned the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials.

Where necessary we contacted trial authors for additional information (February and March 2018).

Data collection and analysis

Selection of studies

Two review authors (DSR and IAR) independently assessed each reference identified by the search against the inclusion criteria. We resolved any disagreements by discussion. We consulted a third author (DO) as an arbiter if we could not reach agreement. We retrieved text in full for those references which appeared to meet the inclusion criteria, for further independent assessment by the same three review authors.

Data extraction and management

We used a predefined form to extract data (Appendix 6). We extracted the following data: eligibility criteria; demographics (age, gender, and country); rate of ascent (metres/hour); final altitude reached (metres); Acute Mountain Syndrome scale; study design; history of high altitude illness (HAI); type of HAI; intervention; and outcomes. For eligible studies, four review authors in two groups (DSR–IAR and DO–YX) extracted the data using the form. We resolved discrepancies through discussion or, when required, we consulted a fifth author (RH). We entered data into Review Manager 5 (RevMan 5) software (Review Manager 2014), and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to obtain further details.

Assessment of risk of bias in included studies

We used Cochrane's tool for assessing risk of bias, a two-part tool that addresses six specific domains: random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective reporting; and other bias (Higgins 2011). The first part describes the risk of bias, the second part provides criteria for making judgements about the risk of bias from each of the six domains in the tool. Based on this tool, we implemented a 'Risk of bias' worksheet to be completed for included studies. We used bias definitions from Porta 2008 for coding the "Other sources of bias" domain. The risk of bias was assessed by four review authors in two groups (DSR–IAR and DO–YX). We resolved any disagreement through consultation with an additional author (RH or JVAF). We displayed the results by creating a 'Risk of bias' graph, and a 'Risk of bias' summary figure using Review Manager 5 software (Review Manager 2014). We present the risk of bias in the Results section. We also provide summary assessments of the risk of bias for each outcome within and across studies (see Characteristics of included studies and Risk of bias in included studies).

Measures of treatment effect

We reviewed the evidence separately for the different interventions. For the binary outcomes (all-cause mortality, complete relief of AMS symptoms, and adverse events), we presented results as summary risk ratios with 95% confidence intervals (95% CI). For continuous outcomes (reduction in illness severity scores) we reported the results as standardized mean difference with 95% CI instead of a mean difference as planned in the published protocol. This is a change from the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Unit of analysis issues

The unit of analysis was the patient. We collected and analysed a single measurement for each outcome from each participant.

Dealing with missing data

In the case of missing data on participants or missing statistics (such as standard deviations (SD)) we planned to contact the trial authors. If unsuccessful, we planned to base our main analysis on the number reaching follow-up, but we planned to perform a sensitivity analysis for worst and best case scenarios. For all outcomes we carried out analyses, as far as possible, on an intention-to-treat basis; that is we planned to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We planned to evaluate the extent of heterogeneity by visual inspection of the forest plot, and to use the I^2 statistic to quantify it (Higgins 2003; Higgins 2011), investigating possible causes of heterogeneity through subgroup analysis. If pre-specified subgroup analyses did not explain the statistical heterogeneity, we planned to perform a sensitivity analysis in which small studies would be excluded. However, due to the scarcity of information we were not able to perform the subgroup analysis. This is a change from the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Assessment of reporting biases

Where we suspected reporting bias, we planned to contact study authors asking them to provide missing outcome data. When this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. We also planned to assess whether the review was subject to publication bias by using a funnel plot to graphically illustrate variability between trials. If asymmetry was detected, we planned to explore causes other than publication bias. We planned to conduct a funnel plot if 10 or more RCTs were included in the review. However, due to the scarcity of information we were not able to

perform these analyses. This is a change from the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Data synthesis

We planned to summarize the findings using both fixed-effect and random-effects models. In the presence of statistical heterogeneity, and an absence of small-study effects, we expected the 95% CI from the random-effects model to include the 95% CI from the fixed-effect model. In this case, we planned to report only the data using the random-effects model as it appropriately conveys heterogeneity. If a substantial difference was observed between both models, we planned to investigate this further as it can be due to an association between effect size and sample size. However, due to the scarcity of information we were not able to perform this analysis. This is a change from the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Subgroup analysis and investigation of heterogeneity

We anticipated clinical heterogeneity in the effect of the intervention and we intended to conduct the following subgroup analyses, if the data were available.

1. Final altitude (metres)
2. High altitude illness history
3. The state of pre-acclimatization
4. The regular intake of medication
5. Pre-existing disease

We planned to perform subgroup analysis only for primary outcomes. However, due to the scarcity of information, we were not able to perform this analysis. This is a change from the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Sensitivity analysis

We planned to conduct a sensitivity analysis comparing the results using all trials as follows.

1. For those RCTs with high methodological quality (studies classified as having a 'low risk of bias' (Higgins 2011)), we planned to choose three core domains instead of all: generation of allocation sequence, incomplete outcome data, and selective reporting bias.
2. For dichotomous outcomes, we planned to conduct ‘best-case’ and ‘worst-case’ scenarios. The ‘best-case’ scenario is that all participants with missing outcomes in the experimental intervention group had good outcomes and all those with missing outcomes in the control intervention group had poor outcomes; the ‘worst-case’ scenario is the converse (Higgins 2011).

We also planned to evaluate the risk of attrition bias, as estimated by the percentage of participants lost to follow-up. Those studies with a total attrition of more than 20% or where differences between the groups exceed 10%, or both, would be included in the review but excluded from the meta-analysis trials. However, due to the scarcity of information we were not able to perform this analysis. This is a change from the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

'Summary of findings' tables and GRADE

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes (Guyatt 2008): all-cause mortality, by high altitude pulmonary oedema (HAPE), or by high altitude cerebral oedema (HACE); complete relief of acute mountain syndrome (AMS) symptoms; reduction in illness severity scores; and adverse events (safety). We developed 'Summary of findings’ (SoF) tables using GRADE software (GRADEpro GDT) for the comparisons.

1. Non-pharmacological interventions for treating acute high altitude illness (Summary of findings for the main comparison).
2. Pharmacological interventions for treating acute high altitude illness (Summary of findings 2).

The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias. We downgraded the evidence one level or two taking into account these criteria. When imprecision was one of the reasons to downgrade the evidence, we provide the corresponding optimal information size calculations in Appendix 7.

We generated a 'Summary of findings' table for each of the interventions stated in the protocol where we found studies reporting the primary outcome: all-cause mortality and complete relief of AMS symptoms. The 'Summary of findings' tables provide outcome-specific information concerning the overall quality of evidence, the magnitude of effect of the interventions examined, and the amount of available data on the outcomes we considered.

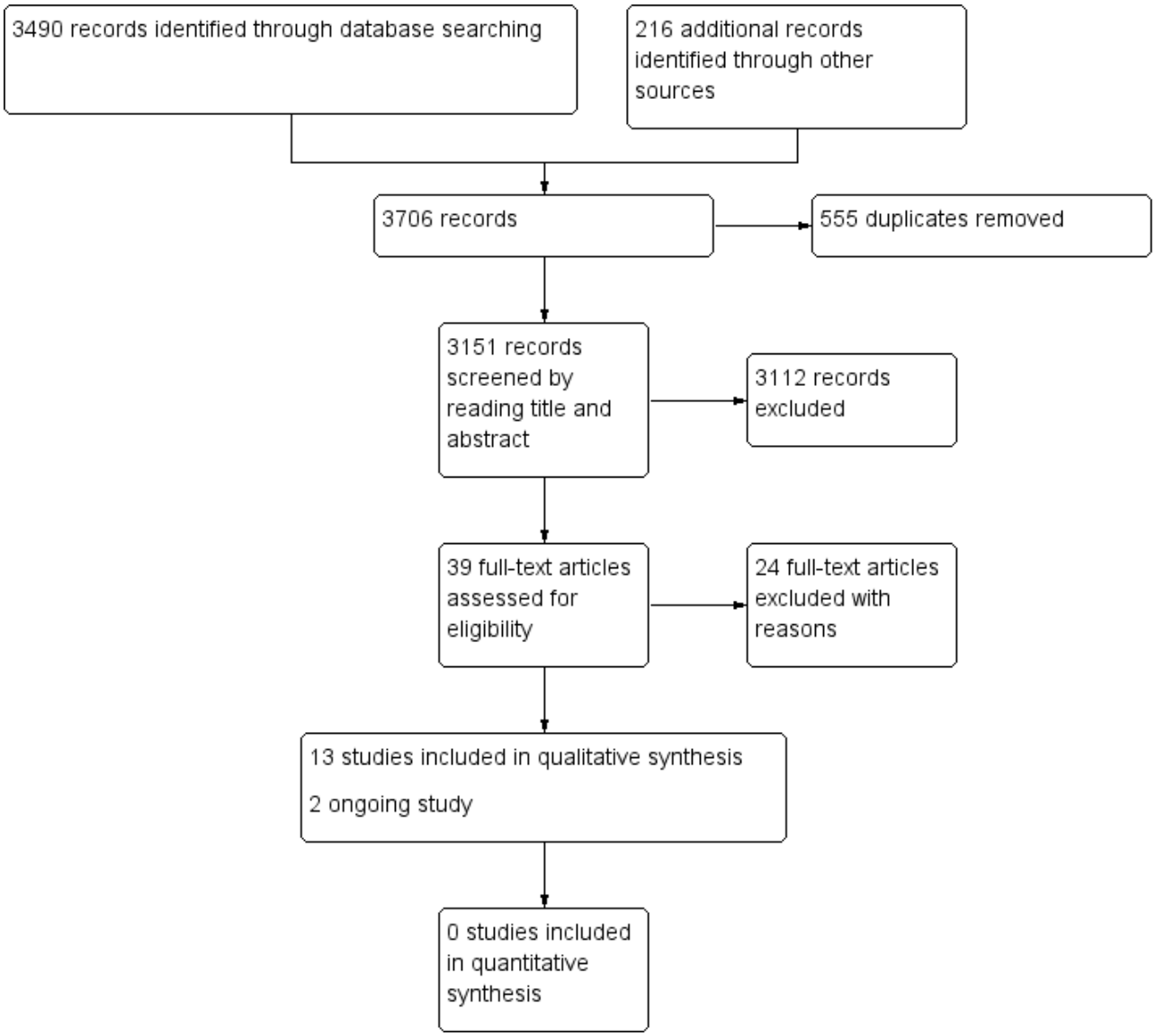
RESULTS

Description of studies

Results of the search

Figure 1 shows the review flow chart.

Figure 1. Study flow diagram.



We ran the search in August 2017 and it yielded 3706 records. We identified 3490 records through database searching, and retrieved 216 references from other sources. We excluded 555 duplicated references, leaving 3151 unique references. We screened the unique references by reading titles and abstracts. From these 3151 references, we identified 39 potentially eligible citations that we reviewed in full text, from which we excluded 24. Of the remaining 15 references, we identified 13 studies of high altitude illness (HAI) which met the inclusion criteria (published in 13 articles), and two ongoing studies (ChiCTR-TRC-13003298; NCT01522326).

Included studies

We included 13 studies (468 participants) in the review (Bärtsch 1990; Bärtsch 1993; Dumont 2004; Ferrazzini 1987; Grissom 1992; Harris 2003; Jafarian 2007a; Kasic 1991; Keller 1995; Li 2006; Utiger 2002; Wang 1998; Wright 1994). See also Characteristics of included studies tables.

Study design

All studies were parallel RCTs. The number of participants varied between 12 (Grissom 1992), and 74 (Harris 2003).

Participants

The proportion of men in the studies ranged from 40% (Harris 2003), to 95% (Bärtsch 1990), except for two studies that included only men (Li 2006; Wang 1998). Distribution by sex was not reported in two studies (Dumont 2004; Wright 1994). In most of the studies the participants were adults aged 18 years old or more. However, two studies also included teenagers (Harris 2003; Li 2006). The age of participants ranged from 13 to 61 years old. Three studies did not report the age distribution (Dumont 2004; Ferrazzini 1987; Wright 1994).

Studies included participants with mild to more severe symptoms of acute high altitude illness, and used different scores to define HAI as inclusion criteria (see Appendix 8). For instance, Wang

1998 recruited participants with HAPE using the definition of high altitude illnesses set forth by the Ad Hoc Committee on High Altitude Illnesses of Chinese Medical Association (Chinese Medical Association 1996). This score is different to the Lake Louise score.

Setting

Six studies took place in the Swiss–Italian border region (Bärtsch 1990; Bärtsch 1993; Dumont 2004; Ferrazzini 1987; Keller 1995; Utiger 2002). The remaining studies were carried out in Alaska (Grissom 1992), the USA (Kasic 1991), Nepal (Harris 2003), Iran (Jafarian 2007a), Tibet (Li 2006), and China (Wang 1998). One study took place in the border areas between China, India and Pakistan (Wright 1994).

Two studies were carried out at high altitude (1500 to 3500 metres; Kasic 1991; Wright 1994), and the remaining in very high altitude (3500 to 5500 metres). No studies were done at extreme altitude (above 5500 metres).

Interventions

A variety of interventions were assessed in the studies. Non-pharmacological intervention studies were limited to the hyperbaric chamber (Bärtsch 1993; Kasic 1991; Keller 1995), while pharmacological interventions were: oxygen (Bärtsch 1990), acetazolamide (Grissom 1992; Wright 1994), dexamethasone (Ferrazzini 1987; Keller 1995; Li 2006; Wang 1998), ibuprofen (Harris 2003), paracetamol (Harris 2003), sumatriptan (Utiger 2002), inhaled nitric oxide (Li 2006; Wang 1998), gabapentin (Jafarian 2007a), nifedipine (Wang 1998), and magnesium (Dumont 2004). Other drugs were included as part of the control group, such as aminophylline (Li 2006; Wang 1998), and furosemide (Li 2006; Wang 1998). We found no studies assessing descent, portable pressure bags or breathing systems.

Six studies were placebo controlled (Dumont 2004; Ferrazzini 1987; Grissom 1992; Jafarian 2007a; Utiger 2002; Wright 1994). The remaining seven studies used a treatment control group. The control group was described as standard care in two studies. The standard care was a combination of aminophylline and dexamethasone plus furosemide (Li 2006), or plus furosemide and oxygen (Wang 1998).

Funding sources

The majority of studies were funded by medical societies, universities or grants from governments or hospitals. In four studies, the private companies that developed the evaluated technologies provided financial support for the study (Harris 2003; Jafarian 2007a; Utiger 2002; Wright 1994). Only in Harris 2003 was there a statement about the independent control of the study by the researchers.

Outcomes

From the four outcomes predefined in the protocol, none of the included studies reported all-cause mortality. Only two studies reported the proportion of participants who experienced a complete relief of symptoms (Ferrazzini 1987; Grissom 1992). All of the studies bar Wang 1998 evaluated reduction in illness severity scores. Utiger 2002 also used a headache score (0 = none, 1 = mild, 2 = moderate, 3 = severe headache), while Harris 2003 and Jafarian 2007a used a standard visual analogue scale (VAS). Four studies reported whether or not participants experienced adverse events (Dumont 2004; Grissom 1992; Jafarian 2007a; Kasic 1991).

In most of the RCTs the follow-up was of 24 hours or less. The exceptions were Li 2006 and Wright 1994, who reported a follow-up of three and five days, respectively; and Wang 1998, where follow-up was until recovery.

Excluded studies

We excluded 24 studies for the following reasons: non-randomized trials, narrative review, preventive studies or did not meet other eligibility criteria (Anand 1998; Bärtsch 1992; Bärtsch 1994; Bates 2007; Benedetti 2015; Bradwell 1988; Broome 1994; Brown 1977; Burtscher 1995; Deshwal 2012; Fagenholz 2007; Forster 1982; Forwand 1968; Levine 1989; Li 2010; Maggiorini 1995; Meehan 1986; Oelz 1989; Oelz 1992; Roggla 2001; Wright 1988; Yan 2010; Yanamandra 2016; Zhang 2012).

See the table Characteristics of excluded studies for further details.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We identified two ongoing studies. ChiCTR-TRC-13003298 aims to assess the effect of oral trimetazidine for reducing the symptoms of acute mountain sickness and improving exercise performance. However, the information provided in the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch), is not clear enough to allow us to define eligibility and we have not found any related publications. The second study is taking place in Nepal, and compares ibuprofen with metoclopramide (NCT01522326) (see Characteristics of ongoing studies).

Risk of bias in included studies

The risk of bias in terms of allocation, blinding, outcome, reporting, and other criteria is summarized in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

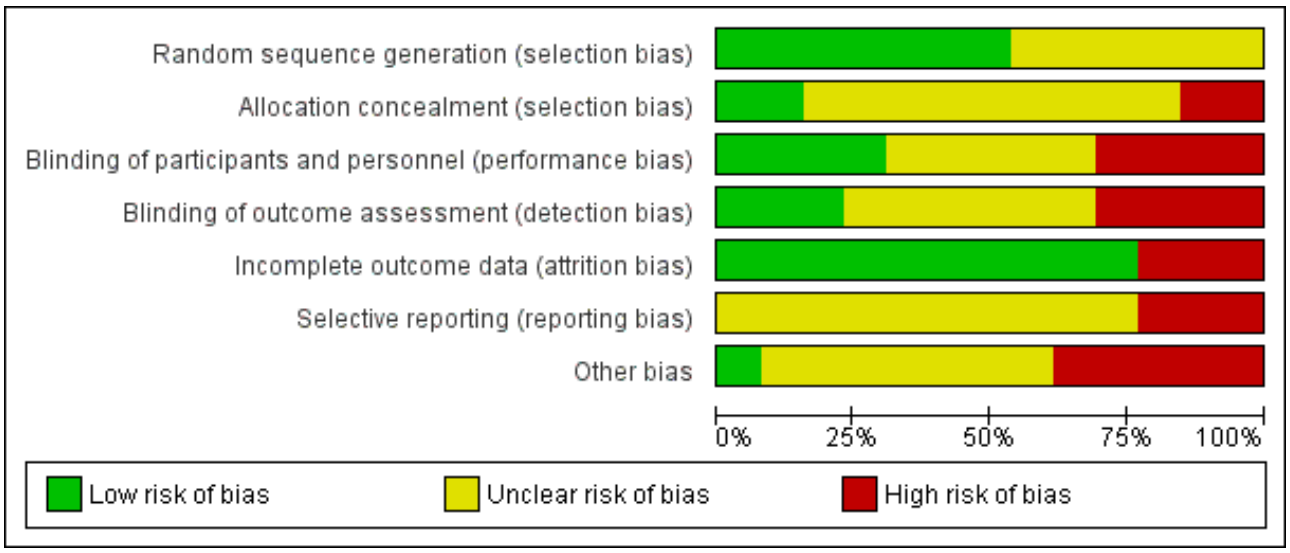
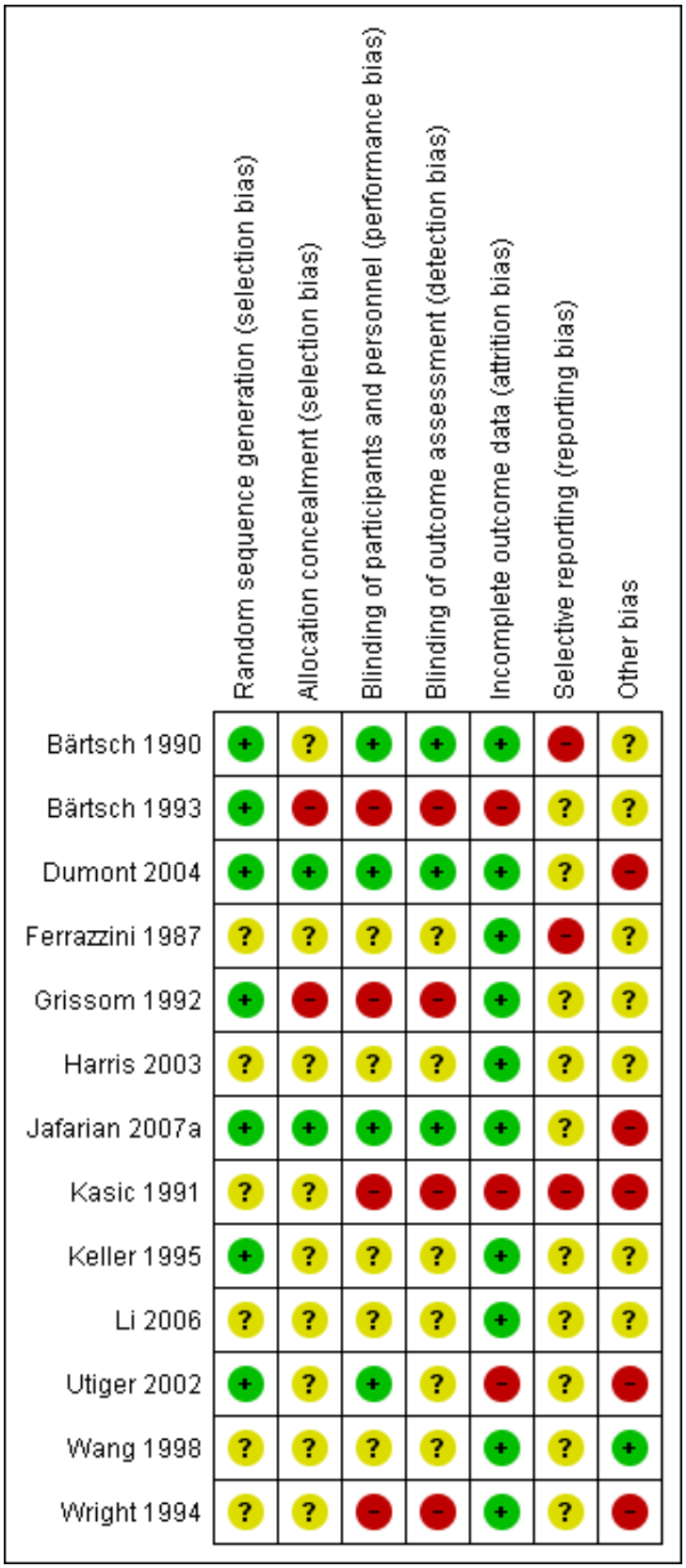


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Seven studies had low risk of selection bias. Two studies used random sequence generation to minimize selection bias, either by using a random number table (Dumont 2004), or computer-generated randomization codes (Jafarian 2007a). In five studies randomization was performed in blocks (Bärtsch 1990; Bärtsch 1993; Grissom 1992; Keller 1995; Utiger 2002).

Six studies did not provide enough information to assess the sequence generation (Ferrazzini 1987; Harris 2003; Kasic 1991; Li 2006; Wang 1998; Wright 1994).

Allocation concealment

Two studies explicitly reported how the allocation was concealed: in Jafarian 2007a the computer-generated randomization codes were exclusively kept by the pharmacist; and in Dumont 2004 the random numbers table was used centrally by the Hospital's Pharmacy. Two studies seem to have compromised allocation concealment: in Grissom 1992, a participant allergic to sulfa-drug was manually assigned to the placebo group; and in Bärtsch 1993, the researcher manually adjusted the order of to-be-assigned blocks. The remaining studies did not provide enough information regarding allocation concealment to assess the risk of bias.

Blinding

Performance bias

Four studies had appropriate blinding methods for participants and personnel (Bärtsch 1990; Dumont 2004; Jafarian 2007a Utiger 2002). Four studies had high risk of bias for this domain considering the subjectivity of the outcomes assessed: two were not blinded (Bärtsch 1993; Kasic 1991); and authors from two studies stated that blinding was compromised during the study (Grissom 1992; Wright 1994). The remaining studies did not provide adequate data to allow assessment of blinding.

Detection bias

Three studies had appropriate methods of blinding assessment outcome (Bärtsch 1990; Dumont 2004; Jafarian 2007a). Four studies had high risk of bias for this domain: two were not blinded in spite of evidently different interventions (Bärtsch 1993; Kasic 1991); and in two studies blinding was compromised (Grissom 1992; Wright 1994). The remaining studies did not provide adequate data to allow assessment of blinding.

Incomplete outcome data

Most of the studies had low risk of attrition bias. The studies provided detailed characteristics of the recruited participants and followed up throughout their trials. Three studies had high risk of bias for this domain: one study, though the authors did not report any withdrawal, reported a small number of participants at the end of the study (Utiger 2002). In Bärtsch 1993, a subgroup of participants were excluded after randomization. And in the third study there was incomplete outcome data due to errors that occurred in the monitoring equipment (Kasic 1991).

Selective reporting

We had not enough information to determine if there was a high risk of bias from selective reporting, since the protocol was not available for any of them. Moreover, we considered three studies to be at high risk of selective reporting because outcome data was presented only graphically (Bärtsch 1990; Ferrazzini 1987; Kasic 1991).

Other potential sources of bias

One study had low risk of other potential bias (Wang 1998). However, seven studies inadequately reported the research design, such as sample size calculation, or had not reported sources of funding; therefore we considered them as having an unclear risk of bias (Bärtsch 1990; Bärtsch 1993; Ferrazzini 1987; Grissom 1992; Harris 2003; Keller 1995; Li 2006).

Five studies were judged to have high risk of bias (Dumont 2004; Jafarian 2007a; Kasic 1991; Utiger 2002; Wright 1994). In Utiger 2002, there were baseline differences after randomization (all females were in the placebo group). In two studies, the potential carry-over effect was a source of bias since participants in the reported study had sequentially participated in a previous trial (Dumont 2004; Wright 1994).

Effects of interventions

See: **Summary of findings for the main comparison** Non-pharmacological interventions for treating acute high altitude illness; **Summary of findings 2** Pharmacological interventions for treating acute high altitude illness

See Summary of findings for the main comparison; Summary of findings 2.

We have obtained some of the numerical results below from graphs in the included papers rather than numerical results given in the text. We have indicated in the results below when this has been done.

Group 1: non-pharmacological interventions

Primary outcomes

All-cause mortality (comparison 1, outcome 1.1)

We found no trials reporting this outcome when using the following non-pharmacological interventions: descent from altitude; use of a portable pressure bag (Gamow Bag); breathing systems for oxygen delivery; or the use of positive airway pressure. In addition, we identified three studies which compared the use of a hyperbaric chamber to simulate descent (Bärtsch 1993; Kasic 1991; Keller 1995), enrolling a total of 124 participants (26% of the total in this review), and none specifically stated that mortality was an outcome of interest. No deaths were reported.

Complete relief of acute mountain sickness symptoms (comparison 1, outcome 2.1)

We found no trials reporting this outcome when using the following non-pharmacological interventions: descent from altitude; use of a portable pressure bag (Gamow Bag); use of a hyperbaric chamber; breathing systems for oxygen delivery; or the use of positive airway pressure.

Secondary outcomes

Reduction in illness severity scores of acute mountain syndrome (comparison 1, outcome 3.1)

We found no trials reporting this outcome when using the following non-pharmacological interventions: descent from altitude; use of a

portable pressure bag (Gamow Bag); breathing systems for oxygen delivery; or the use of positive airway pressure.

3.1 Hyperbaric chamber simulated descent

Three studies reported this outcome, enrolling a total of 124 participants (26% of the total in this review). No pooling of data was possible however, due to clinical heterogeneity arising from the use of different comparators in each trial.

Kasic 1991 included 29 participants, and compared a pressurization of 120 mmHg (equivalent to 160 millibars) versus supplementary oxygen. Clinical outcome data was only presented graphically. For the pressurization group, the estimated score mean is near to 0.7; and for the oxygen group it is near to 0.8 (data estimated from Kasic 1991, Figure 2). The authors stated that both groups had a reduction in symptom scores compared to baseline but there were no important differences between groups.

Bärtsch 1993 included 64 participants, and compared simulated descent using a pressure of 193 millibars versus a pressure of 20 millibars, with a third group in which participants had bed rest. This trial reported both a clinical score, and the Acute Mountain Syndrome - Cerebral (AMS-C) score, a subscore of the Environmental Symptoms Questionnaire developed by Sampson 1983. The AMS-C score was measured after one hour and 12 hours of treatment, as well as at rest. There were no clear differences in the clinical severity scores between the three trial groups 12 hours after treatment (pressure increases of 193 millibar group (mean = 2.5), 20 millibar group (mean = 3.1), and rest only (mean = 2.3); estimated reduction of 0.6 points); or in terms of the AMS-C score (pressure increases of 193 millibar group (mean = 1.02), 20 millibar group (mean = 1.36), and rest only (mean = 0.92)). We downgraded the quality of evidence from high to low due to risk-of-bias issues as well as imprecision (Summary of findings for the main comparison).

Keller 1995 included 31 participants, and compared simulated descent using a pressure of 193 millibars with dexamethasone. This trial reported a reduction in clinical score at one hour when a hyperbaric chamber was compared with dexamethasone (mean of −4.0 points and −1.5 points, respectively). Similar results were found when Lake Louise Score, and AMS-C score were analysed. However, after 11 hours the clinical scores in the simulated descent group were higher than in those who had received dexamethasone (mean of −1.0 and −4.1, respectively; higher results mean worse symptoms).

Adverse events (comparison 1, outcome 4.1)

We found no trials reporting this outcome when using the following non-pharmacological interventions: descent from altitude; use of a portable pressure bag (Gamow Bag); breathing systems for oxygen delivery; or the use of positive airway pressure.

4.1. Hyperbaric chamber simulated descent

Kasic 1991 included 29 participants, and stated there were no complications associated with the use of the hyperbaric chamber (no events in either arm). We downgraded the quality of evidence from high to low due to risk of bias and imprecision issues (Summary of findings for the main comparison).

Group 2: pharmacological interventions

Primary outcomes

All-cause mortality (comparison 2, outcome 2.1)

We found no trials specifically reporting this outcome when using the following pharmacological interventions: oxygen; carbonic anhydrase inhibitors; glucocorticosteroids; non-steroidal anti-inflammatory drugs and acetaminophen; selective 5-HT(1) antagonists; inhaled nitric oxide; anticonvulsant drugs; diuretics; calcium channel blockers; phosphodiesterase inhibitors; or magnesium.

Complete relief of acute mountain sickness symptoms (comparison 2, outcome 2.2 and 2.3)

We found no trials specifically reporting this outcome when using the following pharmacological interventions: oxygen; carbonic anhydrase inhibitors; selective 5-HT(1) antagonists; inhaled nitric oxide; anticonvulsant drugs; diuretics; calcium channel blockers; phosphodiesterase inhibitors; or magnesium.

2.2. Non-steroidal anti-inflammatories and paracetamol

Grissom 1992 enrolled 12 participants (3% of the total in this Cochrane Review), and compared the NSAID ibuprofen 400 mg with paracetamol 1000 mg (six participants to each). At 24 hours five out of six (83%) participants in the ibuprofen group were healthy, compared to none (0%) of the six participants in the paracetamol group (estimated RR 11, CI 95% 0.74 to 163.4).

2.3. Glucocorticosteroids

Ferrazzini 1987 enrolled 35 participants (3% of the total in this Cochrane Review), 17 (49%) allocated to dexamethasone and 18 (51%) to a placebo. Eight out of 17 (47%) participants treated with dexamethasone had all symptoms and signs of acute mountain sickness resolved (score 0) after 12 and 16 hours, compared to none of the 18 (0%) participants who had received placebo (RR not estimable). We downgraded the quality of evidence from high to low due to risk of bias and imprecision issues (Summary of findings 2).

Secondary outcomes

Reduction in illness severity scores of acute mountain syndrome (comparison 2, outcomes 2.4 to 2.11)

We found no trials specifically reporting this outcome when using the following pharmacological interventions: carbonic anhydrase inhibitors; diuretics; calcium channel blockers; or phosphodiesterase inhibitors.

2.4. Oxygen

Bärtsch 1990 enrolled 13 participants (3% of the total in this Cochrane Review) in the comparison of 33% oxygen (six participants, 46%) and a control group breathing normal compressed air (seven participants, 54%). This trial reported that the oxygen group had a greater decrease in the AMS-C score compared with the normal air group (estimated mean score after treatment = 1.1 versus 1.0; data estimated from Bärtsch 1990, figure 1).

2.5. Carbonic anhydrase inhibitors

Two studies reported this outcome, enrolling a total of 25 participants, 5% of the total number of participants included in this

Cochrane Review (Grissom 1992; Wright 1994). There was no clear benefit from the use of acetazolamide compared to placebo (SMD 1.15 lower with acetazolamide, 95% CI 2.56 lower to 0.27 higher; I^2 = 58%; Analysis 1.1). We downgraded the quality of evidence from high to low due to risk of bias, and inconsistency issues (Summary of findings 2).

2.6. Glucocorticosteroids

Ferrazzini 1987 enrolled 35 participants (7.5% of the total in this Cochrane Review), 17 (49%) allocated to dexamethasone and 18 (51%) to a placebo. The mean AMS score dropped from 5.4 (SD 1.7) to 1.3 in the dexamethasone group, and from 4.8 (SD 1) to 4.2 (SD 2.2). Authors reported that the change in the acute mountain sickness score was 4.1 in the dexamethasone group, and 0.4 in the placebo group, a difference of 3.7 units between these groups (SD for each group not reported; confidence interval of the mean difference reported by authors = −5.3 to −2.2). We downgraded the quality of evidence from high to moderate due to the risk of bias (Summary of findings 2).

2.7. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol

Harris 2003 enrolled 74 participants (16% of the total in this Cochrane Review), and compared the NSAID ibuprofen 400 mg (39 (53%) participants) with paracetamol 1000 mg (35 (47%) participants). At one hour, there were no differences in the mean score between the ibuprofen group (mean = 1.8; SD = 1.69), and the paracetamol group (mean = 2.1; SD = 2.18). Within two hours of treatment, the mean of headache intensity was lower in both groups, but there were no differences between the ibuprofen (mean = 0.8; SD = 1.38), and the paracetamol group (mean = 0.9; SD = 1.6).

2.8. Selective 5-hydroxytryptamine (1) receptor agonist

Utiger 2002 enrolled 29 participants (6% of the total in this Cochrane Review), and compared sumatriptan in 14 participants (48%) with a placebo in 15 participants (52%). This trial reported that the headache score decreased significantly in both study groups at one, three and 12 hours after medication. However, there were no significant differences between sumatriptan and placebo at any particular moment of the trial: within three hours the mean score in sumatriptan group was 1.5 (SD = 0.9) versus 1.7 (SD = 1.1) in the placebo group. Within 12 hours (n = 20) sumatriptan mean was 1.5 (SD = 1.1) versus 1.7 for the placebo group (SD = 0.9).

2.9. Inhaled nitric oxide

Li 2006 enrolled 47 participants (10% of the total participants in this Cochrane Review) with 24 (51%) allocated to receive nitric oxide compared to 23 (49%) allocated to a control treatment. Authors reported that both groups had a reduction in symptom scores using the Lake Louise Score, with a mean of 1.78 for the nitric oxide group (SD 1.31) versus a mean of 2.43 for the standard care group (SD 1.56).

2.10. Anticonvulsant drugs

Jafarian 2007a enrolled 24 participants (5% of the total participants in this Cochrane Review), 12 to each of a gabapentin group and a placebo group. Within one hour of treatment there were no differences in the mean VAS score between the gabapentin group (mean = 2.92; SD = 2.91), and the placebo group (mean = 4.75; SD = 3.11. Mean difference not reported by trial authors). We downgraded the quality of evidence from high to low due to risk of bias, and imprecision issues (Summary of findings 2).

2.11. Magnesium

Dumont 2004 enrolled 25 participants (5% of the total in this Cochrane Review) with 12 (48%) allocated to receive magnesium and 13 (52%) to receive a placebo preparation. Authors reported that the mean scores of both groups at two hours were comparable (magnesium sulphate mean score = 9; SD = 3.5; placebo mean score = 10.3; SD = 2.8. Mean difference not reported by trial authors). We downgraded the quality of evidence from high to low due to risk of bias, and imprecision issues (Summary of findings 2).

Adverse events (outcome 2 and outcomes 2.12)

We found no trials specifically reporting this outcome when using the following pharmacological interventions: oxygen; glucocorticosteroids; non-steroidal anti-inflammatory drugs and acetaminophen; selective 5-HT(1) antagonists; inhaled nitric oxide; diuretics; calcium channel blockers; or phosphodiesterase inhibitors.

2.12. Carbonic anhydrase inhibitors

Grissom 1992 stated that no significant adverse events of acetazolamide were found (0% for acetazolamide arm; data not reported for placebo arm; RR not estimable). We downgraded the quality of evidence from high to low due to risk of bias and imprecision issues (Summary of findings 2).

2.13. Anticonvulsant drugs

Jafarian 2007a enrolled 24 participants (5% of the total participants in this Cochrane Review), 12 to each assessed group. The authors reported no adverse events (0% for both arms; RR not reported by trial authors). We downgraded the quality of evidence from high to low due to risk of bias, and imprecision issues (Summary of findings 2).

2.14. Magnesium

Dumont 2004 enrolled 25 participants (5% of the total in this Cochrane Review) with 12 (48%) allocated to receive magnesium and 13 (52%) to receive a placebo preparation. Authors reported that 9 out of 12 participants who had received intravenous magnesium sulphate had flushing, compared to 1 out of 13 participants who had received placebo (75% versus 7%, respectively; RR not reported). We downgraded the quality of evidence from high to low due to risk of bias and imprecision issues (Summary of findings 2).

DISCUSSION

Summary of main results

We retrieved 3706 articles through our search strategy. After applying the eligibility criteria, we included 13 studies and 468 participants in the review, and classified two studies as ongoing. We found sparse evidence from small trials evaluating a wide variety of treatments for high altitude illness (HAI). All studies included adults, and two studies included both teenagers and adults. The 13 studies took place in high altitude areas, mostly in the European Alps. Twelve studies included participants with acute mountain sickness, and one study included participants with high altitude pulmonary oedema. Follow-up was usually less than one day. We report results for the main comparisons as follows.

Non-pharmacological interventions (3 studies, 124 participants)

All-cause mortality, and complete relief of AMS symptoms were not reported for included trials. Regarding reduction in symptom score severity, we found for simulated descent of 193 millibars versus 20 millibars mean scores (read from graphs) of 2.5 and 3.1 after 12 hours of treatment, respectively (one study; 64 participants; low quality of evidence). In addition, no complications were found with use of hyperbaric chambers versus supplementary oxygen (one study; 29 participants; low-quality evidence).

Pharmacological interventions (11 trials, 375 participants)

All-cause mortality was not reported for included trials. One trial found a greater proportion of participants with complete relief of AMS symptoms after 12 and 16 hours when dexamethasone was administered in comparison with placebo (47.1% versus 0%, respectively; RR not estimable; one study; 35 participants; low quality of evidence). Likewise, data on acetazolamide versus placebo did not show differences in terms of reduction in symptom score severity (standardized mean difference (SMD) −1.15, 95% CI −2.56 to 0.27; 2 studies, 25 participants; low-quality evidence). One trial found benefits, in terms of reduction in symptom score severity, when dexamethasone is compared to placebo (difference on change in the AMS score: 3.7 units, reported by authors; one study; 35 patients; moderate quality of evidence). Two additional trials on gabapentin versus placebo, and magnesium versus placebo did not find reductions in symptom score severity at the end of the treatment. (For gabapentin versus placebo: mean VAS score of 2.92 versus 4.75, respectively; one study; 24 participants; low quality of evidence. For magnesium versus placebo: mean scores of 9 and 10.3 units, respectively; one study; 25 participants; low quality of evidence). Regarding adverse effects after treatment, trials comparing acetazolamide versus placebo and gabapentin versus placebo did not find adverse events. (For acetazolamide trial: one study; 25 participants; low quality of evidence; for gabapentin trial: one study; 24 participants; low quality of evidence). One trial comparing magnesium sulphate versus placebo found that flushing was a frequent event in the magnesium arm. (Percentage of flushing: 75% versus 7.7%, respectively; one study; 25 participants; low quality of evidence).

We found no studies addressing interventions such as descent, portable pressure bag or Gamow bag, breathing system designed to conserve oxygen supplies at high altitude, positive airway pressure, aspirin or medroxyprogesterone.

Overall completeness and applicability of evidence

The evidence supporting or refuting the usefulness of a wide range of approaches to treating HAI is incomplete. We identified a limited number of studies addressing the effectiveness and safety of potential interventions to management of acute high altitude illness (13 studies, and 468 participants). Most of the studies did not include participants suffering from high altitude pulmonary oedema (HAPE), and none of the included studies assessed the treatment of high altitude cerebral oedema (HACE). HAPE and HACE are the most severe forms of high altitude illness (HAI). Therefore we have insufficient evidence of the effects of interventions for these conditions. Furthermore, the only study which included participants suffering from HAPE did not report the most severe outcome — mortality. Likewise, the identification of only one study for several assessed comparisons was a common scenario, which limited the ability to address the objectives of this review.

Few included studies reported our primary and secondary outcomes of interest. In addition, we found a variable definition of "standard care" across the included studies. In some cases, the control "standard care" included the use of oxygen, furosemide and aminophylline. This fact may lead to challenges when extrapolating the evidence to practice, since they may not reflect the standard care provided in other settings or countries. We also found the report of outcomes was not complete in many studies. Some studies reported composite outcomes for "cure" which included radiographic findings, and clinical findings. These results are difficult to interpret since we cannot ascertain how much of this definition was based on radiographic or clinical findings.

Quality of the evidence

We used the GRADE system to assess the quality of the body of evidence associated with primary and secondary outcomes. See Summary of findings for the main comparison and Summary of findings 2 for complete assessments and the rationale for ratings. We downgraded the quality of evidence in most cases due to risk of bias as well as imprecision (optimal information size (OIS) was not met due to insufficient sample sizes). In addition, most of the included studies were poorly reported in methodology and outcome data. The poor reporting may be due to the fact that more than half of the studies (8 out of 13) were conducted in the 1980s and 1990s when standards for reporting had not yet been proposed. This explains that a great number of domains in the risk of bias assessment had an "unclear" judgment. Blinding in most cases was not clear or reported as not possible; this fact may limit the interpretation of the study findings, since most of the outcomes were measured with symptomatic scores reported by participants. In addition, funding was a source of bias in a group of studies, and the independence of the research teams was not guaranteed. For further details on the risk of bias, see the Risk of bias in included studies. Finally we could not address the risk of publication bias with a statistical approach, since we did not find enough studies to perform a statistical analysis. However we found no evidence supporting the suspicion of publication bias (e.g. completed clinical trials in registries not published).

Potential biases in the review process

We followed the methodology for systematic reviews outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed a comprehensive search of the evidence for high altitude illness (HAI). Nevertheless, the reports were often incomplete and the attempts at requesting clarification were unsuccessful. Additionally, a single author performed data extraction and risk of bias assessment for the studies reported in Chinese; nevertheless, the results were discussed with the whole review team.

When considering study results, most of the results were narrative as supplied in the paper in question, since meta-analysis was not possible due to clinical heterogeneity. Finally, we did not include observational studies for the assessment of the incidence of adverse events (See Differences between protocol and review). The report of adverse events in the included randomized controlled trials was limited, and therefore this review might not adequately assess this outcome comprehensively.

Agreements and disagreements with other studies or reviews

We found other systematic reviews addressing pharmacological interventions for high altitude illness (Murdoch 2010; Seupaul 2012; Tang 2014; Xu 2014); but all these systematic reviews included randomized controlled trials which evaluated preventive measures, but not treatment, for HAI. Considering the underlying common pathophysiological pathway, many interventions used for prevention are also used for treatment (See Nieto Estrada 2017 for an assessment of pharmacological interventions commonly used for prevention of high altitude illness).

AUTHORS' CONCLUSIONS

Implications for practice

The assessment of non-pharmacological and pharmacological interventions for treating acute high altitude illness suggests there is little evidence available concerning effectiveness and safety of these interventions. Low-quality evidence suggests that dexamethasone and acetazolamide may reduce AMS score compared to placebo. However, clinical benefits and harms related to these potential interventions remain unclear. Overall, the evidence is of limited practical significance in the clinical field.

Implications for research

High-quality research in this field is needed, since most trials were poorly conducted and reported. Blinding of participants, personnel and outcome assessors are key for the evaluation of the subjective symptoms of altitude illness. Mortality should be reported in all trials, especially in those with participants suffering from the most severe forms of altitude illness. The reduction or resolution of high altitude illness symptoms alongside the incidence of adverse events are critical outcomes to inform clinical practice. Consensus on the definition of "standard of care" could improve comparability of trial results. Sample size calculation could improve precision of the effect measures. Adherence to the CONSORT statement and protocol registration/publication could reduce uncertainty when assessing risk of bias domains.

ACKNOWLEDGEMENTS

We would like to thank to Professor Arturo Martí-Carvajal (protocol author) for planning the review and writing the protocol (Martí-Carvajal 2012). We also would like to thank Mike Bennett (content editor), Cathal Walsh (statistical editor), Alex Wright and Edward T Gilbert-Kawai (peer reviewers), Matiram Pun (consumer referee), and Andrew Smith (sign-off editor) for their help and editorial advice during the preparation of this systematic review. Our thanks also to Jane Cracknell for all her support and advice during the editorial process.

Daniel Simancas-Racines is a PhD candidate at the Department of Pediatrics, Gynecology and Obstetrics, and Preventive Medicine, Universitat Autònoma de Barcelona, Spain.

REFERENCES

References to studies included in this review

Bärtsch 1990 *{published data only}*

Bärtsch P, Baumgartner RW, Waber U, Maggiorini M, Oelz O. Comparison of carbon-dioxide-enriched, oxygen-enriched, and normal air in treatment of acute mountain sickness. *Lancet* 1990;**336**(8718):772-5. [PUBMED: 1976147]

Bärtsch 1993 *{published data only}*

Bärtsch P, Merki B, Hofstetter D, Maggiorini M, Kayser B, Oelz O. Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. *BMJ* 1993;**306**(6885):1098-101. [PUBMED: 8495155]

Dumont 2004 *{published data only}*

Dumont L, Lysakowski C, Tramèr MR, Junod JD, Mardirosoff C, Tassonyi E, et al. Magnesium for the prevention and treatment of acute mountain sickness. *Clinical Science* 2004;**106**(3):269-77. [PUBMED: 14572305]

Ferrazzini 1987 *{published data only}*

Ferrazzini G, Maggiorini M, Kriemler S, Bärtsch P, Oelz O. Successful treatment of acute mountain sickness with dexamethasone. *BMJ (Clinical Research Ed.)* 1987;**294**(6584):1380-2. [PUBMED: 3109663]

Grissom 1992 *{published data only}*

Grissom CK, Roach RC, Sarnquist FH, Hackett PH. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Annals of Internal Medicine* 1992;**116**(6):461-5. [PUBMED: 1739236]

Harris 2003 *{published data only}*

Harris NS, Wenzel RP, Thomas SH. High altitude headache: efficacy of acetaminophen vs. ibuprofen in a randomized, controlled trial. *Journal of Emergency Medicine* 2003;**24**(4):383-7. [PUBMED: 12745039]

Jafarian 2007a *{published data only}*

Jafarian S, Gorouhi F, Salimi S, Lotfi J. Low-dose gabapentin in treatment of high-altitude headache. *Cephalalgia* 2007;**27**(11):1274-7. [PUBMED: 17692105]

Kasic 1991 *{published data only}*

Kasic JF, Yaron M, Nicholas RA, Lickteig JA, Roach R. Treatment of acute mountain sickness: hyperbaric versus oxygen therapy. *Annals of Emergency Medicine* 1991;**20**(10):1109-12. [PUBMED: 1928883]

Keller 1995 *{published data only}*

Keller HR, Maggiorini M, Bärtsch P, Oelz O. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *BMJ* 1995;**310**(6989):1232-5. [PUBMED: 7767194]

Li 2006 *{published data only}*

Li S, Zheng B, He Y, Wang H, Li, Qu T. The effect of the therapy on acute high altitude disease by inhaling nitrogen monoxidum air balanced in plateau. *Journal of Chinese Physician* 2006;**8**(12):1631-3.

Utiger 2002 *{published data only}*

Utiger D, Eichenberger U, Bernasch D, Baumgartner RW, Bärtsch P. Transient minor improvement of high altitude headache by sumatriptan. *High Altitude Medicine and Biology* 2002;**3**(4):387-93. [PUBMED: 12631424]

Wang 1998 *{published data only}*

Wang W, Zhang X, Ma Y. [Low-concentration nitrous oxide inhalation in the treatment of high-altitude pulmonary edema]. *Chinese Journal of Tuberculosis and Respiratory Diseases* 1998;**21**(4):212-4. [PUBMED: 11326965]

Wright 1994 *{published data only}*

Wright AD, Winterborn MH, Forster PJ, Delamere JP, Harrison GL, Bradwell AR. Carbonic anhydrase inhibition in the immediate therapy of acute mountain sickness. *Journal of Wilderness Medicine* 1994;**5**(1):49-55. [DOI: 10.1580/0953-9859-5.1.49]

References to studies excluded from this review

Anand 1998 *{published data only}*

Anand IS, Prasad BA, Chugh SS, Rao KR, Cornfield DN, Milla CE, et al. Effects of inhaled nitric oxide and oxygen in high-altitude pulmonary edema. *Circulation* 1998;**98**(22):2441-5. [PUBMED: 9832490]

Bärtsch 1992 *{published data only}*

Bärtsch P. Treatment of high altitude diseases without drugs. *International Journal of Sports Medicine* 1992;**13 Suppl 1**:S71-4. [PUBMED: 1483799]

Bärtsch 1994 *{published data only}*

Bärtsch P, Maggi S, Kleger GR, Ballmer PE, Baumgartner RW. Sumatriptan for high-altitude headache. Lancet 1994; Vol. 344, issue 8934:1445. [PUBMED: 7968111]

Bates 2007 *{published data only}*

Bates MG, Thompson AA, Baillie JK. Phosphodiesterase type 5 inhibitors in the treatment and prevention of high altitude pulmonary edema. *Current Opinion in Investigational Drugs (London, England : 2000)* 2007;**8**(3):226-31. [PUBMED: 17408118]

Benedetti 2015 *{published data only}*

Benedetti F, Durando J, Giudetti L, Pampallona A, Vighetti S. High-altitude headache: the effects of real vs sham oxygen administration. *Pain* 2015;**156**(11):2326-36. [PUBMED: 26164587]

Bradwell 1988 *{published data only}*

Bradwell AR, Winterborn M, Wright AD, Forster PE, Dykes PW. Acetazolamide treatment of acute mountain sickness [abstract]. *Clinical Science* 1988;**74**(Suppl 18):62P. [CENTRAL: CN-00258335]

Broome 1994 *{published data only}*

Broome JR, Stoneham MD, Beeley JM, Milledge JS, Hughes AS. High altitude headache: treatment with ibuprofen. *Aviation, Space, and Environmental Medicine* 1994;**65**(1):19-20. [PUBMED: 8117220]

Brown 1977 *{published data only}*

Spironolactone in acute mountain sickness. Lancet (London, England) 1977; Vol. 1, issue 8016:855. [PUBMED: 67358]

Burtscher 1995 *{published data only}*

Burtscher M, Likar R, Nachbauer W, Schaffert W, Philadelphy M. Ibuprofen versus sumatriptan for high-altitude headache. Lancet (London, England) 1995; Vol. 346, issue 8969:254-5. [PUBMED: 7616830]

Deshwal 2012 *{published data only}*

Deshwal R, Iqbal M, Basnet S. Nifedipine for the treatment of high altitude pulmonary edema. *Wilderness & Environmental Medicine* 2012;**23**(1):7-10. [PUBMED: 22441082]

Fagenholz 2007 *{published data only}*

Fagenholz PJ, Gutman JA, Murray AF, Harris NS. Treatment of high altitude pulmonary edema at 4240 m in Nepal. *High Altitude Medicine & Biology* 2007;**8**(2):139-46. [PUBMED: 17584008]

Forster 1982 *{published data only}*

Forster P. Methazolamide in acute mountain sickness. Lancet (London, England) 1982; Vol. 1, issue 8283:1254. [PUBMED: 6123014]

Forwand 1968 *{published data only}*

Forwand SA, Landowne M, Follansbee JN, Hansen JE. Effect of acetazolamide on acute mountain sickness. *New England Journal of Medicine* 1968;**279**(16):839-45. [PUBMED: 4877992]

Levine 1989 *{published data only}*

Levine BD, Yoshimura K, Kobayashi T, Fukushima M, Shibamoto T, Ueda G. Dexamethasone in the treatment of acute mountain sickness. *New England Journal of Medicine* 1989;**321**(25):1707-13. [PUBMED: 2687688]

Li 2010 *{published data only}*

Li SZ, Zheng BH, Yan CC, Wang YL, Zeng JB, Chen B, et al. Four therapeutic regimens for high altitude pulmonary edema: result comparison and preliminary study of standardized treatment. *Medical Journal of National Defending Forces in Southwest China* 2010;**20**(7):771-4.

Maggiorini 1995 *{published data only}*

Maggiorini M, Merki B, Pallavicini E, Bärtsch P, Oelz O. Acetazolamide and almitrin in the treatment of acute mountain sickness [Acetozolamid und Almitrin bei Behandlung der akuten Bergkrankheit]. *Schweizerische Medizinische Wochenschrift* 1995;**125**(Suppl 69):55. [CENTRAL: CN-00307575]

Meehan 1986 *{published data only}*

Meehan RT, Cymerman A, Rock P, Fulco CS, Hoffman J, Abernathy C, et al. The effect of naproxen on acute mountain sickness and vascular responses to hypoxia. *American Journal of the Medical Sciences* 1986;**292**(1):15-20. [PUBMED: 3521277]

Oelz 1989 *{published data only}*

Oelz O, Maggiorini M, Ritter M, Waber U, Jenni R, Vock P, et al. Nifedipine for high altitude pulmonary oedema. *Lancet* 1989;**2**(8674):1241-4. [PUBMED: 2573760]

Oelz 1992 *{published data only}*

Oelz O, Maggiorini M, Ritter M, Noti C, Waber U, Vock P, et al. Prevention and treatment of high altitude pulmonary edema by a calcium channel blocker. *International Journal of Sports Medicine* 1992;**13 Suppl 1**:S65-8. [PUBMED: 1483797]

Roggla 2001 *{published data only}*

Roggla G, Domej W, Roggla M. Does theophylline really improve acute mountain sickness?. European Respiratory Journal 2001; Vol. 17, issue 3:575. [PUBMED: 11405540]

Wright 1988 *{published data only}*

Wright AD, Bradwell AR. Cerebral blood flow in acute mountain sickness and treatment with acetazolamide [abstract]. *Clinical Science* 1988;**74**(Suppl 18):1. [CENTRAL: CN-00258251]

Yan 2010 *{published data only}*

Yan Ch, Li S, Wang Y, Zheng B, Zheng J, Chen B, et al. Three therapeutic regimens for high altitude cerebral edema:result comparison and preliminary study of standardized treatment [高原脑水肿不同治疗方案的疗效比较及其规范化治疗初步探讨]. *Medical Journal of National Defending Forces in Southwest China* 2010;**20**(7):774-7.

Yanamandra 2016 *{published data only}*

Yanamandra U, Nair V, Singh S, Gupta A, Mulajkar D, Yanamandra S, et al. Managing high-altitude pulmonary edema with oxygen alone: results of a randomized controlled trial. *High Altitude Medicine and Biology* 2016;**17**(4):294-9. [PUBMED: 27906598]

Zhang 2012 *{published data only}*

Zhang XF, Ma SQ, Wu SZ, Yang ZP, Chen Q. [Bundle program of treatment for acute severe type high altitude disease]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue = Chinese Critical Care Medicine* 2012;**24**(7):415-8. [PUBMED: 22748458]

References to ongoing studies

ChiCTR-TRC-13003298 *{published data only}*

ChiCTR-TRC-13003298. Oral trimetazidine for reducing the symptoms of acute mountain sickness and improving exercise performance. www.chictr.org.cn/showprojen.aspx?proj=6261 first received 29 June 2013.

NCT01522326 *{unpublished data only}*

NCT01522326. Comparison of metoclopramide and ibuprofen for the treatment of acute mountain sickness. clinicaltrials.gov/ct2/show/NCT01522326 first received 31 January 2012.

Additional references

Adams 2004

Adams J. Ginkgo biloba and acetazolamide for acute mountain sickness: exclusion of high risk, low status groups perpetuates discrimination and inequalities. *BMJ (Clinical Research Ed.)* 2004;**329**(7458):171; author reply 172. [PUBMED: 15258082]

Austin 1998

Austin D. Gammow bag for acute mountain sickness. *Lancet* 1998;**351**(9118):1815. [PUBMED: 9635981]

Bailey 2009

Bailey DM, Bärtsch P, Knauth M, Baumgartner RW. Emerging concepts in acute mountain sickness and high-altitude cerebral edema: from the molecular to the morphological. *Cellular and Molecular Life Sciences* 2009;**66**(22):3583-94. [PUBMED: 19763397]

Basnyat 2003

Basnyat B, Murdoch DR. High-altitude illness. *Lancet* 2003;**361**(9373):1967-74. [PUBMED: 12801752]

Blitzer 1996

Blitzer ML, Loh E, Roddy MA, Stamler JS, Creager MA. Endothelium-derived nitric oxide regulates systemic and pulmonary vascular resistance during acute hypoxia in humans. *Journal of the American College of Cardiology* 1996;**28**(3):591-6. [PUBMED: 8772744]

Burtscher 2001

Burtscher M, Likar R, Nachbauer W, Philadelphy M, Puhringer R, Lammle T. Effects of aspirin during exercise on the incidence of high-altitude headache: a randomized, double-blind, placebo-controlled trial. *Headache* 2001;**41**(6):542-5. [PUBMED: 11437888]

Bärtsch 2004

Bärtsch P, Bailey DM, Berger MM, Knauth M, Baumgartner RW. Acute mountain sickness: controversies and advances. *High Altitude Medicine & Biology* 2004;**5**(2):110-24. [PUBMED: 15265333]

Bärtsch 2013

Bärtsch P, Swenson ER. Acute high-altitude illnesses. *New England Journal of Medicine* 2013;**369**(17):1666-7. [PUBMED: 24152275]

Canoui-Poitrine 2014

Canoui-Poitrine F, Veerabudun K, Larmignat P, Letournel M, Bastuji-Garin S, Richalet JP. Risk prediction score for severe high altitude illness: a cohort study. *PloS One* 2014;**9**(7):e100642. [PUBMED: 25068815]

CATMAT 2007

CATMAT. Statement on high-altitude illnesses. An Advisory Committee Statement (ACS). Committee to Advise on Tropical Medicine and Travel (CATMAT). *Canada Communicable Disease Report = Releve des Maladies Transmissibles au Canada* 2007;**33**(ACS-5):1-20. [PUBMED: 17520777]

CDC Yellow Book 2016

Centers for Disease Control and Prevention. CDC Health Information for International Travel 2016. New York: Oxford University Press, 2016.

Cheng 2006

Cheng JK, Chiou LC. Mechanisms of the antinociceptive action of gabapentin. *Journal of Pharmacological Sciences* 2006;**100**(5):471-86. [PUBMED: 16474201]

Chinese Medical Association 1996

Third Ad Hoc Committee on High Altitude Illnesses of Chinese Medical Association. Consensus statement for the criteria for the denomination, classification and diagnosis of high altitude illnesses in China. *Tibetan Medicine Journal* 1996;**17**:1-3.

Dehnert 2010

Dehnert C, Bärtsch P. Can patients with coronary heart disease go to high altitude?. *High Altitude Medicine & Biology* 2010;**11**(3):183-8. [PUBMED: 20919884]

Eide 2012

Eide RP 3rd, Asplund CA. Altitude illness: update on prevention and treatment. *Current Sports Medicine Reports* 2012;**11**(3):124-30. [PUBMED: 22580489]

Elphick 2004

Elphick HL, Elphick DA. Ginkgo biloba and acetazolamide for acute mountain sickness: bias in participants may underestimate effectiveness of agents. BMJ (Clinical research edition) 2004; Vol. 329, issue 7458:172; author reply 172. [PUBMED: 15258084]

Fisher 2000

Fischer R, Lang SM, Steiner U, Toepfer M, Hautmann H, Pongratz H, et al. Theophylline improves acute mountain sickness. *European Respiratory Journal* 2000;**15**(1):123-7. [PUBMED: 10678632]

Freeman 2004

Freeman K, Shalit M, Stroh G. Use of the Gamow bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. *Wilderness & Environmental Medicine* 2004;**15**(3):198-201. [PUBMED: 15473460]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version access August 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians?. *BMJ (Clinical Research Ed.)* 2008;**336**(7651):995-8. [PUBMED: 18456631]

Hackett 1988

Hackett PH, Roach RC, Wood RA, Foutch RG, Meehan RT, Rennie D, et al. Dexamethasone for prevention and treatment

of acute mountain sickness. *Aviation, Space, and Environmental Medicine* 1988;**59**(10):950-4. [PUBMED: 3190622]

Hackett 1992

Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD. The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: a comparison. *International Journal of Sports Medicine* 1992;**13 Suppl 1**:68-71. [PUBMED: 1483798]

Hackett 2004

Hackett PH, Roach RC. High altitude cerebral edema. *High Altitude Medicine & Biology* 2004;**5**(2):136-46. [PUBMED: 15265335]

Hall 2011

Hall DP, Duncan K, Baillie JK. High altitude pulmonary oedema. *Journal of the Royal Army Medical Corps* 2011;**157**(1):68-72. [PUBMED: 21465914]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)* 2003;**327**(7414):557-60. [PUBMED: 12958120]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hill 1909

Hill L. An oxygen generator and inhaler: its use in mountain sickness. *British Medical Journal* 1909;**2**(2552):1522-4. [PUBMED: 20764764]

Hultgren 1975

Hultgren HN. Letter: Furosemide for high altitude pulmonary edema. *JAMA* 1975;**234**(6):589-90. [PUBMED: 1242183]

Höhne 2007

Höhne C, Pickerodt PA, Francis RC, Boemke W, Swenson ER. Pulmonary vasodilation by acetazolamide during hypoxia is unrelated to carbonic anhydrase inhibition. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 2007;**292**(1):L178-84. [PUBMED: 16936246]

Imray 2010

Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: pathophysiology, prevention, and treatment. *Progress in Cardiovascular Diseases* 2010;**52**(6):467-84. [PUBMED: 20417340]

Jafarian 2007b

Jafarian S, Gorouhi F, Salimi S, Lotfi J. Sumatriptan for prevention of acute mountain sickness: randomized clinical trial. *Annals of Neurology* 2007;**62**(3):273-7. [PUBMED: 17557349]

Koch 2009

Koch RO, Hinterhuber L, Faulhaber M, Gatterer H, Graupner S, Muenzel K, et al. A successful therapy of high-altitude pulmonary edema with a CPAP helmet on Lenin Peak. *Clinical Journal of Sport Medicine* 2009;**19**(1):72-3. [PUBMED: 19124989]

Larson 1992

Larson EB. Positive airway pressure for high-altitude pulmonary oedema. *Lancet* 1985;**1**(8425):371-3. [PUBMED: 2857423]

Leaf 2007

Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. Journal of Applied Physiology 2007; Vol. 102, issue 4:1313-22. [PUBMED: 17023566]

Leissner 2009

Leissner KB, Mahmood FU. Physiology and pathophysiology at high altitude: considerations for the anesthesiologist. *Journal of Anesthesia* 2009;**23**(4):543-53. [PUBMED: 19921365]

León-Velarde 2010

León-Velarde F, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. *Progress in Cardiovascular Diseases* 2010;**52**(6):540-9. [PUBMED: 20417348]

Luks 2010

Luks AM, McIntosh SE, Grissom CK, Auerbach PS, Rodway GW, Schoene RB, et al. Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness & Environmental Medicine* 2010;**21**(2):146-55. [PUBMED: 20591379]

Luks 2014

Luks AM, McIntosh SE, Grissom CK, Auerbach PS, Rodway GW, Schoene RB, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 update. *Wilderness & Environmental Medicine* 2014;**25**(4 Suppl):S4-14. [PUBMED: 25498261]

Luks 2017

Luks AM, Swenson ER, Bartsch P. Acute high-altitude sickness. *European Respiratory Review* 2017;**26**(143):1-14. [PUBMED: 28143879]

Maggiorini 2010

Maggiorini M. Prevention and treatment of high-altitude pulmonary edema. *Progress in Cardiovascular Diseases* 2010;**52**(6):500-6. [PUBMED: 20417343]

Maneuf 2006

Maneuf YP, Luo ZD, Lee K. Alpha2 delta and the mechanism of action of gabapentin in the treatment of pain. *Seminars in Cell & Developmental Biology* 2006;**17**(5):565-70. [PUBMED: 17067834]

Monge 1942

Monge C. Life in the Andes and chronic mountain sickness. *Science (New York, N.Y.)* 1942;**95**(2456):79-84. [PUBMED: 17757318]

Murata 2004

Murata T, Hori M, Sakamoto K, Karaki H, Ozaki H. Dexamethasone blocks hypoxia-induced endothelial dysfunction in organ-cultured pulmonary arteries.

American Journal of Respiratory and Critical Care Medicine 2004;**170**(6):647-55. [PUBMED: 15184203]

Murata 2005

Murata T, Suzuki N, Yamawaki H, Sato K, Hori M, Karaki H, et al. Dexamethasone prevents impairment of endothelium-dependent relaxation in arteries cultured with fetal bovine serum. *European Journal of Pharmacology* 2005;**515**(1-3):134-41. [PUBMED: 15907323]

Murdoch 2010

Murdoch D. Altitude sickness. *BMJ Clinical Evidence* 2010;**2010**:1209. [PUBMED: 21718562]

Nebeker 2004

Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of Internal Medicine* 2004;**140**(10):795-801. [PUBMED: 15148066]

Nieto Estrada 2017

Nieto Estrada VH, Molano Franco D, Medina RD, Gonzalez Garay AG, Martí-Carvajal AJ, Arevalo-Rodriguez I. Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs. *Cochrane Database of Systematic Reviews* 2017, Issue 6. [DOI: 10.1002/14651858.CD009761.pub2]

Palmer 2010

Palmer BF. Physiology and pathophysiology with ascent to altitude. *American Journal of the Medical Sciences* 2010;**340**(1):69-77. [PUBMED: 20442648]

Paralikar 2010

Paralikar SJ, Paralikar JH. High-altitude medicine. *Indian Journal of Occupational and Environmental Medicine* 2010;**14**(1):6-12. [PUBMED: 20808661]

Pasha 2010

Pasha MA, Newman JH. High-altitude disorders: pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest* 2010;**137 Suppl 6**:13-9. [PUBMED: 20522576]

Pattinson 2005

Pattinson KT, Somogyi RB, Fisher JA, Bradwell AR. Efficient breathing circuit for use at altitude. *Wilderness & Environmental Medicine* 2005;**16**(2):101-3. [PUBMED: 15974260]

Porta 2008

Porta M. A Dictionary of Epidemiology. 5th Edition. London: Oxford University Press, 2008.

Pubchem - Furosemide 2017

National Center for Biotechnology Information – Pubchem: Open Chemistry Database. Furosemide $C_{12}H_{11}ClN_2O_5S$ - Compound summary for CID 3440 [Internet]. pubchem.ncbi.nlm.nih.gov/compound/furosemide [cited 20 February 2017].

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ri-Li 2003

Ri-Li G, Chase PJ, Witkowski S, Wyrick BL, Stone JA, Levine BD, et al. Obesity: associations with acute mountain sickness. *Annals of Internal Medicine* 2003;**139**(4):253-7. [PUBMED: 12965980]

Roach 1993

Roach RC, Bärtsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Surron JR, Houston CS, Coates G editor(s). Hypoxia and Molecular Medicine. Burlington: Queen City Printers Inc., 1993:272-4.

Sampson 1983

Sampson JB, Cymerman A, Burse RL, Maher JT, Rock PB. Procedures for the measurement of acute mountain sickness. *Aviation, Space, and Environmental Medicine* 1983;**54**(12 Pt 1):1063-73. [PUBMED: 6661120]

Scherrer 1996

Scherrer U, Vollenweider L, Delabays A, Savcic M, Eichenberger U, Kleger GR, et al. Inhaled nitric oxide for high-altitude pulmonary edema. *New England Journal of Medicine* 1996;**334**(10):624-9. [PUBMED: 8592525]

Scherrer 2010

Scherrer U, Rexhaj E, Jayet PY, Allemann Y, Sartori C. New insights in the pathogenesis of high-altitude pulmonary edema. *Progress in Cardiovascular Diseases* 2010;**52**(6):485-92. [PUBMED: 20417341]

Schoene 1985

Schoene RB, Roach RC, Hackett PH, Harrison G, Mills WJ Jr. High altitude pulmonary edema and exercise at 4,400 meters on Mount McKinley. Effect of expiratory positive airway pressure. *Chest* 1985;**87**(3):330-3. [PUBMED: 3882350]

Schoene 2004

Schoene RB. Unraveling the mechanism of high altitude pulmonary edema. *High Altitude Medicine & Biology* 2004;**5**(2):125-35. [PUBMED: 15265334]

Schoene 2008

Schoene RB. Illnesses at high altitude. *Chest* 2008;**134**(2):402-16. [PUBMED: 18682459]

Seupaul 2012

Seupaul RA, Welch JL, Malka ST, Emmett TW. Pharmacologic prophylaxis for acute mountain sickness: a systematic shortcut review. *Annals of Emergency Medicine* 2012;**59**(4):307-17.e1. [PUBMED: 22153998]

Smedley 2013

Smedley T, Grocott MP. Acute high-altitude illness: a clinically orientated review. *British Journal of Pain* 2013;**7**(2):85-94. [PUBMED: 26516505]

Stream 2008

Stream JO, Grissom CK. Update on high-altitude pulmonary edema: pathogenesis, prevention, and treatment. *Wilderness & Environmental Medicine* 2008;**19**(4):293-303. [PUBMED: 19099331]

Tang 2014

Tang E, Chen Y, Luo Y. Dexamethasone for the prevention of acute mountain sickness: systematic review and meta-analysis. *International Journal of Cardiology* 2014;**173**(2):133-8. [PUBMED: 24679688]

Wang 2003

Wang T, El Kebir D, Blaise G. Inhaled nitric oxide in 2003: a review of its mechanisms of action. *Canadian Journal of Anaesthesia/Journal canadien d'anesthésie* 2003;**50**(8):839-46. [PUBMED: 14525827]

Windsor 2009

Windsor JS, Firth PG, Grocott MP, Rodway GW, Montgomery HE. Mountain mortality: a review of deaths that occur during recreational activities in the mountains. *Postgraduate Medical Journal* 2009;**85**(1004):316-21. [PUBMED: 19528307]

Wright 2004

Wright AD, Beazley MF, Bradwell AR, Chesner IM, Clayton RN, Forster PJ, et al. Medroxyprogesterone at high altitude. The effects on blood gases, cerebral regional oxygenation, and acute mountain sickness. *Wilderness & Environmental Medicine* 2004;**15**(1):25-31. [PUBMED: 15040503]

Wright 2008

Wright A, Brearey S, Imray C. High hopes at high altitudes: pharmacotherapy for acute mountain sickness and high-altitude cerebral and pulmonary oedema. *Expert Opinion on Pharmacotherapy* 2008;**9**(1):119-27. [PUBMED: 18076343]

Xu 2014

Xu Y, Liu Y, Liu J, Qian G. Meta-analysis of clinical efficacy of sildenafil, a phosphodiesterase type-5 inhibitor on high altitude hypoxia and its complications. *High Altitude Medicine & Biology* 2014;**15**(1):46-51. [PUBMED: 24673534]

Yang 2007

Yang B, Wang GY, Chen B, Qin RB, Xi SL, Chen L. Anti-hypoxia and anti-oxidation effects of aminophylline on human with acute high-altitude exposure. *Chinese Medical Sciences Journal* 2007;**22**(1):62-5. [PUBMED: 17441321]

Zafren 1996

Zafren K, Reeves JT, Schoene R. Treatment of high-altitude pulmonary edema by bed rest and supplemental oxygen. *Wilderness & Environmental Medicine* 1996;**7**(2):127-32. [PUBMED: 11990106]

Zafren 1998

Zafren K. Gamow bag for high-altitude cerebral oedema. Lancet 1998; Vol. 352, issue 9124:325-6. [PUBMED: 9690443]

References to other published versions of this review

Martí-Carvajal 2012

Martí-Carvajal AJ, Simancas-Racines D, Hidalgo R. Interventions for treating high altitude illness. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD009567]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bärtsch 1990

Methods	**Two-group parallel RCT, 1 centre** **ITT**: no **Overall study quality**: high risk of bias **Unit of randomization**: assignment of gas composition was randomized in blocks of 9 **Follow-up period:** 24 h "all investigations were carried out within a day after arrival at 4559 m" **Diagnosis of AMS** 1. Acute mountain sickness (AMS) score. “A score of more than 3 was required for entry to the trial” **Scale used for assessing AMS** 1. Subscore (AMS-C) including 11 statements (Appendix 8) 2. Environmental symptom questionnaire (Appendix 8)
Participants	**Number of participants randomized**: 20 **Sex**: men = 19 (95%)

Bärtsch 1990 *(Continued)*

	Age: median 32 years (range 22 to 51) **Baseline data** 1. Not reported **Inclusion criteria** 1. Patients with an AMS score more than 3 **Exclusion criteria** 1. Not clearly reported
Interventions	**Intervention group 1 (n = 6)** 1. Oxygen in nitrogen. Dose: 33% (1.6%); route: breathing through a tightly fitted face mask; duration: 30 min; frequency: not clearly reported, apparently a single dose **Intervention group 2 (n = 7)** 1. Carbon dioxide in air. Dose 3% (0.15%); breathing through a tightly fitted face mask; duration: 30 min; frequency: not clearly reported, apparently a single dose **Control group (n = 7)** 1. Compressed "normal" air. Duration: 30 min; frequency: not clearly reported, apparently a single dose **Co-intervention** 1. Room air was provided for 30 min right before the experimental gas. The gas was humidified and the flow adjusted manually to the ventilation of the subject by the maintenance of a 50 litre reservoir-balloon at a constant size
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Severity of AMS (AMS-C score, Appendix 8). Before and immediately after the treatment 2. Symptoms of environmental stress (Appendix 8). After each clinical examination 3. Physiological variables: ventilation, $PaCO_2$, PaO_2, Oxygen saturation 4. Mean blood flow velocity in the median cerebral artery (MCA) **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Swiss–Italian border, Capanna "Regina Margherita" in the Alps Valais **Altitude setting**: 4559 m (barometric pressure 430 mmHg to 440 mmHg) **Study dates**: not reported **Identifier number**: not reported **A priori sample estimation**: no **Conflicts of interest**: not reported **Funding/Support** 1. "This study was supported by grant 3200-0092.85 from the Swiss National Science Foundation"

Risk of bias

Bias	Authors' judgement	Support for judgement

Bärtsch 1990 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "assignment of gas composition was randomised in blocks of nine" (page 773)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the person responsible for the gas supply, the gas bottles, and the reservoir-balloon were hidden behind a curtain from the subjects and the examiners" (page 773)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "four investigators carried out one each of four different measurements throughout the study-clinical examinations, ventilation, blood gas analysis, and transcranial doppler ultrasound examination. They were not aware of each other's results during treatment of any particular patient" (page 773)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	High risk	Results are reported in a figure. Exact numbers could not be retrieved. In the text, authors reported interpretation of data and P values
Other bias	Unclear risk	Bias in the presentation data: baseline characteristics by groups was not shown

Bärtsch 1993

Methods	**Three-group parallel RCT, 1 centre** **ITT**: no **Overall study quality**: high risk of bias **Unit of randomization**: participants **Follow-up period**: 12 h **Diagnosis of AMS** 1. "Headache and one additional sign or symptom were required for entering the trial" **Scales used for assessing acute mountain sickness** 1. Clinical score (Appendix 8) 2. AMS-C score of the questionnaire (Appendix 8)
Participants	**Number of participants randomized:** 64 **Sex**: men = 49 (77%) **Age** : mean 31 years (range 18 to 52) **Baseline data** 1. Clinical score mean: Intervention group — 4.1, 95% CI 3.7 to 4.5; Control group 1 — 4.3, 95% CI 3.7 to 4.8; Control group 2 — 4.5, 95% CI 4.0 to 5.0 2. AMS-C score mean: Intervention group — 1.8, 95% CI 1.5 to 2.2; Control group 1 — 1.6, 95% CI 1.2 to 1.9; Control group 2 — 1.4, 95% CI 0.7 to 2.6

Bärtsch 1993 *(Continued)*

	Inclusion criteria 1. Mountaineers planning to stay overnight "who had ascended by foot and who stayed at 4559 m for at least 12 hours after treatment were eligible to enter the trial if they suffered from headache and one or more additional symptoms of acute mountain sickness". "Headache and one additional sign or symptom were required for entering the trial" **Exclusion criteria** 1. "Subjects with clinical signs of high altitude pulmonary oedema (dyspnoea at rest, respiration rate > 25/min, and rales) and those who had taken acetazolamide or nifedipine during ascent"
Interventions	**Intervention group (n = 31)** 1. Hyperbaric chamber at a pressure of 193 mbar; dose: 193 mbar; frequency: once during the trial; duration of the intervention: 1 h **Control group 1 (n = 23)** 1. Hyperbaric chamber at a pressure of 20 mbar; dose: 20 mbar; frequency: once during the trial; duration of the intervention: 1 h **Control group 2 (n = 10)** 1. Name: bed rest; dose: NA; frequency: once during the trial; duration of the intervention: **Cointervention** 1. Analgesic: paracetamol (intervention group = 18; control group 1 = 15; control group 2 = 8), 2. Antiemetic: thiethylperazine (intervention group = 2; control group 1 = 6; control group 2 = 2) **Characteristics of the chamber: fabric hyperbaric chamber made by Certec (F-692 10 Sourcieux-les-Mines, France)
Outcomes	Do the authors define outcomes as 'primary' or 'secondary'?: yes **Primary** 1. Symptoms of acute mountain sickness before, immediately after, and 12 h after treatment 2. Permitted intake of analgesic 3. Antiemetic drugs in the follow-up period **Secondary** 1. Arterial oxygen saturation **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Swiss–Italian border, Capanna "Regina Margherita" in the Alps Valais **Altitude setting** 4559 m (barometric pressure 430 mmHg to 440 mmHg) **Identifier number**: not reported **Study dates**: 1990 to 1991 **A priori sample estimation**: no **Conflicts of Interest**: not reported **Funding/Support**

Bärtsch 1993 *(Continued)*

1. "This study was supported by a grant from the research institute of the Swiss School of Sports, Magglingen, and by grant 3200-0092.85 from the Swiss National Science Foundation"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed in blocks of six (in 1990) and nine (in 1991)." Page 1098
Allocation concealment (selection bias)	High risk	Quote: "the investigator assigned the treatment by drawing a lot from an envelope containing the assignments of one block. When the remaining lots could be predicted they were added to the envelope containing the next randomisation block." Page 1099
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding method reported. Hyperbaric chamber compared to bed rest has not been masked. Outcomes are dependent on subjective assessment
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding method reported; however, hyperbaric chamber compared to bed rest has not been masked and the outcome is dependent on subjective assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "in 1990 the first seven subjects assigned to low pressure were unintentionally treated with 39 mbar (equivalent to a descent of 500 m) until the inaccuracy of the built in manometer in the low pressure range was discovered. Their results were excluded from analysis, although they were not significantly different from those obtained in subjects treated with 16 or 23 mbar." Page 1099. Outcome data was not available for seven participants in the intervention group (unbalanced attrition)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Protocol not available
Other bias	Unclear risk	The use of analgesics and antiemetics was permitted during the study period as an option in the three groups. Authors found no significant statistical difference among groups in the use of these drugs

Dumont 2004

Methods

Two-group parallel RCT, 1 centre

ITT: no
Overall study quality: high risk of bias

Unit of randomization: participants

Follow-up period

1. Not clearly reported
2. Adverse events were measured up to 90 min after intervention

Diagnosis of AMS

1. Lake Louise Score > 6 with a headache score > 2 and/or a gastrointestinal score > 2 and/or an ataxia score > 2

Dumont 2004 *(Continued)*

Scale used for assessing acute mountain sickness

1. Lake Louise Score (minimum score is 0 and the maximal score is 25)

Participants	**Number of participants randomized**: 25 **Sex**: not reported **Age**: adults, details about age were not reported **Baseline data** 1. AMS Lake Louise score: Intervention group: mean 11.6 (SD = 1.7) 2. Control group: mean 10.9 (SD = 3) **Inclusion criteria** 1. "Subjects from the prevention trial who had consented to take part in the treatment trial providing prevention failed". Prevention failed: "Lake Louise Score > 6 with a headache score > 2 and/or a gastrointestinal score > 2 and/or an ataxia score > 2" 2. "Volunteers at the Capanna Regina Margherita who had not taken part in the prevention trial, but who had a Lake Louise Score > 6 with a headache score > 2 and/or a gastrointestinal score > 2 and/or an ataxia score > 2" **Exclusion criteria** 1. Residency above 600 m 2. A stay above 2000 m 3. Medication, including vitamins or magnesium, during the last 3 months 4. Cardiac, pulmonary, neurological, renal, hepatic or psychiatric disease
Interventions	**Intervention group (n = 12)** **Name**: magnesium sulphate (16 mmol) **Route**: intravenous infusion **Dose**: 4 grams. Ampoules drawn into bags of 100 ml of physiological saline and infused over 30 min **Frequency**: single dose **Duration of the intervention**: infusion for 30 min **Control group (n = 13)** **Name**: matching placebo **Cointerventions** 1. 20 patients (80%) received Magnesium as prophylaxis, in a prevention trial, hours or few days before the treatment trial 2. If the treatment failed, or if the volunteers wished so, they received rescue medication (oxygen by face mask, 4 mg of dexamethasone intravenously and 500 mg of acetazolamide orally)
Outcomes	**Primary** 1. Treatment success. Defined as number of subjects who had a drop in the Lake Louise Score > 50% 60 min after the start of the treatment (i.e. 30 min after the end of the infusion) **Secondary** 1. Number of subjects who had a drop in the Lake Louise Score > 25% and whether or not there was a significant decrease in the score after treatment compared with before the start of the treatment **Adverse effects** 1. Outcomes of interest in the review: reduction in illness severity scores of AMS and adverse events
Notes	**Country**: Swiss-Italian border, Capanna "Regina Margherita" in the Alps Valais

Dumont 2004 *(Continued)*

Altitude setting: 4559 m (barometric pressure 430 mmHg to 440 mmHg)

Identifier number: not reported

Study dates: not reported

A priori sample estimation: yes

Conflicts of interest: not reported

Funding/Support

Study was supported by

1. research funds from the Department of Anaesthesiology, Pharmacology and Surgical Intensive Care, Geneva University Hospitals, Geneva, Switzerland; and
2. the Carlos and Elsie De Reuter Fund, Switzerland

M.R.T.

1. received a Programme for Social Medicine, Preventive and Edpidemiological Research (PROSPER) grant from the Swiss National Science Foundation (No. 3233-051939.97/2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized, placebo-controlled, double-blind trial". "The Geneva University Hospital Pharmacy was responsible for randomization (table of random numbers) and preparation of the study drugs" Page 270
Allocation concealment (selection bias)	Low risk	Quote: "the Geneva University Hospital Pharmacy was responsible for randomization (table of random numbers) and preparation of the study drugs." Comment: Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, placebo-controlled, double-blind trial". Page 270. Quote: "study drugs were provided in identical, numbered 20 ml ampoules" Page 271
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, placebo-controlled, double-blind trial". Page 270. Quote: "study drugs were provided in identical, numbered 20 ml ampoules" Page 271
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Protocol not available.
Other bias	High risk	20 patients (80%) received magnesium as prophylaxis, in a prevention trial, hours or few days before the treatment trial. This may be a confusion variable. It is not clearly stated the timing of rescue medication or the reason (either treatment failure or volunteers' wish)

Ferrazzini 1987

Methods	**Two-group parallel RCT, 1 centre** **ITT**: no **Overall study quality**: high risk of bias **Unit of randomization**: patients **Follow-up period:** unclear, apparently 12 to 16 h **Diagnosis of AMS** 1. 3 or more points in a symptoms severity score **Scale used for assessing Acute Mountain Sickness** 1. The name of the scale is not reported. Authors described "The presence of the symptoms listed was scored as follows: one point for mild headache, nausea, dizziness, shortness of breath and insomnia and two points for severe headache (not relieved by paracetamol 500 mg) and for vomiting. Responses were checked with one of the investigators. Subjects then underwent a clinical examination for tachypnoea (two points), facial or peripheral oedema (one location one point, two or more locations two points), ataxia (heel to toe walking test and Romberg test two points), and pulmonary rales (discreet one point, pronounced two points). Patients with three or more points were selected for the drug trial"
Participants	**Number of participants randomized**: 35 **Sex**: men = 28 (80%) **Age**: "the two groups were comparable in age" **Baseline data (mean symptom score per group)** 1. Dexamethasone group = mean 5.4 (SD = 1.7) 2. Placebo group = mean 4.8 (SD = 1.0) **Inclusion criteria** 1. Climbers with symptoms of acute mountain sickness (AMS: 3 or more points in the in the symptoms severity score) **Exclusion criteria** 1. Frank high altitude pulmonary or cerebral oedema, or both
Interventions	**Intervention group 1 (n = 17)** 1. Dexamethasone, route: by mouth; dose: "8 mg initially and another 4 mg after six and 12 hours"; frequency: initially and then every 6 h; duration of the intervention: 12 to 16 h **Control group (n = 18)** 1. Identical placebo, route: not clearly reported, "identical placebo"; dose: not clearly reported, "identical placebo"; frequency: not clearly reported, "identical placebo"; duration of the intervention: 12 to 16 h **Cointervention** 1. None reported
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Acute mountain sickness score: baseline and after 12 to 16 h of intervention 2. Number of patients becoming totally asymptomatic

Ferrazzini 1987 *(Continued)*

3. Arterial oxygen saturation
4. Spirometric measurements: resting minute ventilation, forced vital capacity, and forced expiratory volume in 1 second
5. Physiological measures: weight, pulse rate, blood pressure, arterial oxygen saturation
6. Retinal photography

Outcomes of interest in the review

1. Complete relief of AMS symptoms
2. Reduction in illness severity scores of AMS

Notes

Country: Swiss–Italian border, Capanna "Regina Margherita" in the Alps Valais

Altitude setting: 4559 m (barometric pressure 430 mmHg to 440 mmHg)

Identifier number: not reported

Study dates: not reported

Priori sample estimation: no

Conflicts of Interest: not reported.

Funding/Support

1. "This study was supported by a grant from the EMDO Stiftung" (University of Zurich)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "patients were randomly assigned". Page 1381
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "patients were randomly assigned". Page 1381
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "A double blind, randomised, placebo controlled trial". Page 1380
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "A double blind, randomised, placebo controlled trial". Page 1380
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	High risk	Protocol not available. Data presented graphically for individuals. No data available for each group for symptomatic scores
Other bias	Unclear risk	Baseline characteristics poorly presented

Grissom 1992

Methods	**Two-group parallel RCT, 1 centre** **ITT**: yes **Overall study quality**: high risk of bias **Unit of randomization**: participants **Follow-up period**: not clearly specified. Probably 24 h after intervention **Diagnosis of AMS** 1. "The AMS Symptom Questionnaire was used to diagnose acute mountain sickness and to evaluate severity" **Scale used for assessing Acute Mountain Sickness** 1. AMS Symptom Questionnaire (not Lake Louise), a weighted severity scale of 1 to 3 (least severe to most severe) with 9 items and a maximum score of 18 (Appendix 8)
Participants	**Number of participants randomized**: 12 **Sex**: men = 10 (91%) **Age**: median 32 years (range 25 to 46) **Baseline data** **Mean symptom scores** 1. Acetazolamide group: 3.8 +/- 0.4 2. Placebo group: 3.8 +/- 1.7 **Inclusion criteria** 1. Patients with acute mountain sickness (score of 2 or greater on a weighted severity scale of 1 to 3), onset of symptoms at 4200 m within 24 h of inclusion **Exclusion criteria** 1. Use of acetazolamide within the previous week, defined high altitude pulmonary oedema or high altitude cerebral oedema, serious medical illness
Interventions	**Intervention group (n = 6)** 1. Acetazolamide. Dose, frequency and duration: 250 mg, at time 0 and 8 h after inclusion in the study. Route: oral **Control group (n = 6)** 1. Placebo. Dose, frequency and duration: at time 0 and 8 h after inclusion in the study. Route: oral **Co-intervention** 1. None reported
Outcomes	**Main outcome measures** 1. Acute mountain sickness score at baseline and at 24 h 2. Pulmonary gas exchange at baseline and at 24 h **Secondary outcomes** 1. Other physiologic measurements 2. Side effects

Grissom 1992 *(Continued)*

Outcomes of interest in the review

1. Complete relief of AMS symptoms
2. Reduction in illness severity scores of AMS
3. Adverse events

Notes

Country: Alaska. Denali Medical Research Project high altitude research station, McKinley

Altitude setting: 4200 m
Identifier number: not reported

Study dates: June 1989

A priori sample estimation: no

Conflicts of Interest: not reported

Funding/Support

1. “In part by the Carles S. Houston Award from the Wilderness Medical Society; the American Heart Association Alaska Affiliate; and the United States Army Research and Development Command”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomly assigned to receive either acetazolamide or placebo in a double-blind fashion". Quote: "randomization was done in blocks of four to ensure equivalent numbers in each group". Page 462
Allocation concealment (selection bias)	High risk	Quote: "one participant reported a history of sulfa-drug allergy and was assigned (non-randomly) to the placebo group" Page 462
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "participants were randomly assigned to receive either acetazolamide or placebo in a double-blind fashion" Page 462. However, authors reported "several participants reported increased urination and suspected that they were receiving acetazolamide" Page 463, this situation may have influenced results like acute mountain sickness score
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. However, authors reported "several participants reported increased urination and suspected that they were receiving acetazolamide" Page 463, this situation may have influenced results like the acute mountain sickness score
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available
Other bias	Unclear risk	Design bias: not sample size calculation

Harris 2003

Methods

Two-group parallel RCT, 1 centre

ITT: yes

Harris 2003 *(Continued)*

	Overall study quality: high risk of bias **Unit of randomization**: climbers **Follow-up period**: 2 h **Scale used for assessing acute mountain sickness score** 1. Lake Louise Acute Mountain Sickness (AMS) criteria **Scale used for assessing high altitude headache** 1. Visual analogue scale (VAS)
Participants	**Number of participants randomized**: 74 **Sex**: men = 30 (40%) **Age**: mean 33 years (range 13 to 61) **Baseline data** 1. **AMS score**: Ibuprofen = 5.9 (SD not reported); paracetamol = 5.9 (SD not reported) 2. **VAS score**: Ibuprofen = 4.9, CI 95% 4.1 to 5.7); paracetamol = 4.7, CI 95% 4.0 to 5.5 **Inclusion criteria** 1. "Trekkers experiencing headache" **Exclusion criteria** 1. History of chronic headache disorder, migraine headache, NSAID/paracetamol allergy, previous use of same within the prior 8 h No cases of HAPE or HACE were noted during the study period
Interventions	**Intervention group 1 (n = 39)** 1. Ibuprofen, route: oral; dose: 400 mg; frequency: not clearly reported, apparently a single dose **Intervention group 2 (n = 35)** 1. Paracetamol, route: oral; dose: 1000 mg; frequency: not clearly reported, apparently a single dose **Cointerventions** 1. Not reported
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Relief high altitude headache 2. VAS at time 0, 30, 60 and 120 min **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Nepal **Altitude setting**: 4243 m **Identifier number**: not reported **Study dates:** not reported **A priori sample estimation**: no

Harris 2003 *(Continued)*

Conflicts of Interest: not reported

Funding/Support

1. "This work was supported through an unrestricted grant provided by McNeil CPC. Absolute control of study design, data acquisition, analysis, and interpretation, as well as manuscript preparation, resided exclusively with the named authors at all times." (Page 383)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "randomly assigned rapid-release capsules" Page 384
Allocation concealment (selection bias)	Unclear risk	Quote: "each was given an envelope containing a detailed history questionnaire, followed by four separate, identical pages containing 10 cm visual analogue scales (VAS). The envelope also contained identical, randomly assigned rapid-release capsules..." Page 384. Comments: it is not stated whether the envelope was opaque or not
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding of participants and personnel to permit judgment of 'Low risk' or High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding of participants and personnel to permit judgment of 'Low risk' or High risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost after randomization: 1 (1%) ("after choosing to leave the study area (decided to hike further during the day"), study group not reported. Outcome data (all outcomes) were available for the rest of the participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available
Other bias	Unclear risk	Design bias: not sample size calculation

Jafarian 2007a

Methods	**Two-group parallel RCT, 1 centre** **ITT**: no **Overall study quality**: low risk of bias **Follow-up period**: 18 h **Scale used for assessing acute mountain sickness score** 1. Lake Louise Acute Mountain Sickness criteria, severity of High Altitude Headache (HAH) based on visual analogue scale pain score (VAS)
Participants	**Number of participants randomized:** 24 **Sex**: men = 14 (58%)

Jafarian 2007a *(Continued)*

Age: mean 29.1 years (SD = 1.7, range 18 to 50 years)

Inclusion criteria

1. ≥ 18 years, suffering high altitude headache before 24 h of ascent

Exclusion criteria

1. Severe cardiac, pulmonary or liver disease
2. Severely impaired kidney function
3. History of migraine
4. Current history of alcohol or drug abuse
5. Allergy to gabapentin
6. Treatment with anticonvulsants or tricyclic antidepressants

Interventions	**Intervention group (n = 12)** 1. Gabapentin; route: oral; dose: 300 mg; frequency: not clearly reported, apparently a single dose; duration of the intervention: not clearly reported, apparently a single dose **Control group (n = 12)** 1. Placebo (monohydrate lactose identical capsule); route: oral; frequency: not clearly reported, apparently a single dose; duration of the intervention: not clearly reported, apparently a single dose **Co-intervention** 1. 400 mg ibuprofen after 1 h of gabapentin/placebo intake (page 1275)
Outcomes	**Primary endpoints** 1. Need of supplementary analgesics after 1 h of gabapentin/placebo 2. Severity of HAH based on VAS score 3. Duration of HAH-free phase **Secondary endpoints** 1. AMS incidence (Lake Louise score ≥ 3 with headache and any other symptom) 2. Incidence of severe AMS (Lake Louise score ≥ 5) **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS and adverse events
Notes	**Country:** Iran (Tochal Hotel) **Altitude setting**: 3500 m **Identifier number**: not reported **Study dates**: 1 to 7 January and 10 to 20 February 2007 **A priori sample estimation**: no **Financial disclosures**: not reported **Funding/Support** 1. Darou Darman Pars Pharmaceuticals (providing gabapentin and placebo)

Risk of bias

Bias	Authors' judgement	Support for judgement

Jafarian 2007a *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "the computer-generated randomisation codes" (page 1275)
Allocation concealment (selection bias)	Low risk	Quote: "only the pharmacist who provided the drugs knew the details of the computer-generated randomisation codes" (page 1275) Quote: "medications were in identical opaque boxes labelled with randomisation codes that were not disclosed to investigators or assessor." (page 1275)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "medications were in identical opaque boxes labelled with randomisation codes that were not disclosed to investigators or assessor." (page 1275)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "medications were in identical opaque boxes labelled with randomisation codes that were not disclosed to investigators or assessor." (page 1275)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available.
Other bias	High risk	"We acknowledge Dr Alireza Madjd, managing director of Darou Darman Pars Pharmaceuticals, for providing gabapentin and placebo". There was no statement addressing the independence of authors with regard to those providing funding (source of industry bias)

Kasic 1991

Methods	**Two-group parallel RCT, 1 centre** **ITT**: no **Overall study quality**: high risk of bias **Unit of randomization**: participants **Follow-up period:** "patients were monitored for only one hour after treatment" **Diagnosis of AMS** 1. "Patients with nausea or headache who had arrived to altitude within 72 hours". Also "AMS patients with mild HAPE as diagnosed by chest radiography and clinical examination" **Scale used for assessing acute mountain sickness** 1. "A mild headache was assigned one point, and two points were given for a severe headache. Nausea was given one point"
Participants	**Number of participants randomized**: 29; "because of mechanical and technical errors, complete data were available in only 24 of the subjects" **Sex**: men = 17 (71%) **Age**: mean 37 years **Baseline data**

Kasic 1991 *(Continued)*

1. 6 participants had AMS and HAPE (hyperbaric chamber = 3; supplementary oxygen = 3).

Inclusion criteria

1. Patients with AMS: "patients with nausea or headache who had arrived to altitude within 72 hours"
2. "AMS patients with mild HAPE as diagnosed by chest radiography and clinical examination"

Exclusion criteria

1. Severe altitude illness (requiring prompt evacuation to a lower-altitude treatment facility)
2. Previous treatment with oxygen, acetazolamide, or dexamethasone
3. Acute or chronic heart or lung disease (not including HAPE)
4. Less than 18 years of age
5. Pregnancy or nursing mother
6. Evidence of acute upper respiratory infection

Interventions	**Intervention group (n = 13)** 1. Hyperbaric chamber (simulated descent of 1432 m) dose: 120 mmHg of pressurisation above ambient pressure; route: breathing air inside the chamber; frequency and duration: 2 h **Control group (n = 11)** 1. Supplementary oxygen; dose: 4 L (30% to 35%); route: by facemask; frequency and duration: 2 h **Co-intervention** 1. None reported
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Symptom response: "symptoms of headache and nausea were monitored at 15-minute intervals for the first hour and at 30-minute intervals for an additional hour of treatment and for one hour after treatment". Symptoms were scored "using the same point system that was used for entry of patients into the study" 2. Speed of symptom resolution 3. Haemodynamic variables: blood pressure, heart rate, arterial oxygen saturation (SaO_2) 4. Complications **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS 2. Adverse events
Notes	**Country:** USA (Snake River Health Clinic, Keystone, Colorado) **Altitude setting**: 2850 m **Identifier number**: not reported **Study dates**: not reported **A priori sample estimation**: no **Conflicts of interest**: not reported **Funding/Support** 1. This study was funded in part by a grant from DuPont de Nemours and Company, Inc, and the University of Colorado Department of Chemical Engineering 2. The chamber was donated to the institute by Hyperbaric Mountain Technologies Inc.

Kasic 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "patients agreeing to participate signed informed consent and then were randomly assigned to oxygen or hyperbaric treatment protocols." Page 1110
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "patients agreeing to participate signed informed consent and then were randomly assigned to oxygen or hyperbaric treatment protocols." Page 1110
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was not blinded. Quote: "we did not attempt to blind either the oxygen or the hyperbaric therapy." Page 1111
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was not blinded. Quote: "we did not attempt to blind either the oxygen or the hyperbaric therapy." Page 1111
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome data was missing from: hyperbaric chamber group = 2 out of 13 (15%) participants; oxygen group = 3 out of 11 (27%) participants. Reason: Quote: "because of mechanical and technical errors, complete data were available in only 24 of the subjects, and the remainder was excluded from data analysis." "These errors occurred in the monitoring equipment, not with the hyperbaric chamber" Page 1111
Selective reporting (reporting bias)	High risk	Protocol not available. Data presented graphically for individuals. No data available for each group for symptomatic scores
Other bias	High risk	Design bias: not sample size calculation There was no statement considering the independence of authors with respect to those providing funding (source of industry bias)

Keller 1995

Methods	**Two-group parallel RCT, 1 centre** **ITT**: yes **Overall study quality**: high risk of bias **Unit of randomization**: patients **Follow-up period**: at least 11 h **Scales for assessing acute mountain sickness score** 1. Lake Louise score, clinical score, and AMS-C score of the environmental symptom questionnaire of Sampson 1983
Participants	**Number of participants randomized**: 31 climbers with symptoms of acute mountain sickness

Keller 1995 *(Continued)*

Sex: men = 22 (71%)

Age: mean 31.5 years

Inclusion criteria

1. Mountaineers planning to stay overnight; symptoms or signs of acute mountain sickness; clinical score of 3 or more for clinical acute mountain sickness

Exclusion criteria

1. Clinical signs of high altitude pulmonary oedema

Quote: "most subjects had ascended to high altitude without prior acclimatisation... by using a cable car to an altitude of 3200." (page 1232)

Interventions	**Intervention group (n = 15)** 1. Name: hyperbaric chamber (Certec, F-69210 Sourcieux-les-Mines, France); dose: 193 mbar (equivalent to a descent of 2250 m); frequency: once during the trial; duration of the intervention: 1 h **Control group (n = 16)** 1. Name: dexamethasone, route: oral administration; dose: 8 mg initially; frequency: 4 mg every 6 h; duration of the intervention: not clearly reported. Due to severe vomiting in 4 subjects the initial dose was administered intravenously **Co-intervention** 1. "After they entered the trial subjects were allowed to take mild analgesics (paracetamol) for headache, but this had to be reported to the investigator"
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Acute mountain sickness relief: Lake Louise score, clinical score and AMS-C score. Measured before the intervention and after 1 h and 11 h 2. Permitted intake of mild analgesics before treatment and in the follow-up period 3. Physiological variables: pulse rate, blood pressure and arterial oxygen saturation **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Swiss–Italian border. Capanna "Regina Margherita" located at an altitude of in the Alps Valais **Altitude setting**: 4559 m (barometric pressure 430 mmHg to 440 mmHg) **Identifier number**: not reported **Study dates**: not reported **A priori sample estimation**: no **Financial disclosures**: not reported **Funding/Support** 1. Swiss National Science Foundation (grant 32-33729.92)

Risk of bias

Bias	Authors' judgement	Support for judgement

Keller 1995 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed in blocks of eight by drawing lots from an envelope containing the assignments of one block." Page 310
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "randomisation was performed in blocks of eight by drawing lots from an envelope containing the assignments of one block." Page 310
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding. Quote: "the volunteers completed a questionnaire on environmental symptoms' and the Lake Louise self assessment questionnaire directed towards the symptoms of acute mountain sickness. The responses were checked with the investigator, and subsequently a clinical examination for peripheral oedema, pulmonary rales, and ataxia (Romberg test and heel to toe walking test) was performed." "Interviews and clinical examinations were always performed by the same investigator" Page 1233
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available
Other bias	Unclear risk	Design bias: not sample size calculation

Li 2006

Methods	**Two-group parallel RCT, 1 centre** **ITT**: no **Overall study quality**: high risk of bias **Unit of randomization**: participants **Follow-up period**: not clearly reported **Diagnosis of AMS** 1. “Patients who met the mountain sickness diagnosis criteria according to the Chinese Medical Association (1996)” **Scale used for assessing acute mountain sickness** 1. Lake Louise questionnaire
Participants	**Number of participants randomized**: 47 **Sex**: men = 47 (100%) **Age**: mean 18 (range 16 to 21) **Baseline data**

Li 2006 *(Continued)*

1. Lake Louise questionnaire: standard intervention group = 4.39 (SD = 2.31), nitric oxide Intervention Group = 4.43 (SD = 2.04)

Inclusion criteria

1. "The patients who met the mountain sickness diagnosis criteria according to the China Plateau Medical Association (1996)"

Exclusion criteria

1. Not reported

Interventions	**Intervention group (n = 24)** 1. Nitric oxide plus standard treatment; route: inhalation; dose: 0.001% nitric oxide, 3 L/min; nitric oxide inhalation balanced with air at 3658 m; frequency: twice/day; duration of the intervention: 1 h/time **Control group (n = 23)** 1. Standard intervention group (oxygen inhalation; aminophylline; dexamethasone; furosemide); route, dose, frequency and duration of the intervention: details not reported **Co-intervention** 1. Not reported
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Change in Lake Louise Score **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Tibet, China **Altitude setting**: 3658 m **Identifier number**: not reported **Study dates**: not reported **A priori sample estimation**: no **Conflicts of Interest**: not reported **Funding/Support** 1. Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "47 male participants were randomised into 2 groups". Page 1631. Authors did not specify if a random sequence generation was used
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'

Li 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available
Other bias	Unclear risk	Design bias: not sample size calculation

Utiger 2002

Methods	**Two-group parallel RCT, 1 centre** **ITT**: yes **Overall study quality**: high risk of bias **Unit of randomization**: participants **Follow-up period**: up to 12 h after medication **Diagnosis of AMS** 1. "Medical history, history of headache at low altitude, headache score and Lake Louise AMS score " **Scale used for assessing Acute Mountain Sickness** 1. Lake Louise AMS score (LL score) 2. Headache score
Participants	**Number of participants randomized**: 29 **Sex**: men = 23 (79%) 1. Sumatriptan group: 14 men 2. Placebo: 9 men + 6 women. Quote " ...all 6 women participating in the study were assigned to the placebo group" (page 389) **Age**: mean 34.5 years (18 to 56 years) **Baseline data** 1. Lake Louise Score: mean 6.1 +/- 1.4 2. Headache score: mean 2.4 +/- 0.5 **Inclusion criteria** 1. Moderate headache on a 4-point scale (0 = none, 1 = light, 2 = moderate, 3 = severe) 2. Stay overnight at the hut 3. Written informed consent

Utiger 2002 *(Continued)*

Exclusion criteria

1. Age under 18 or over 55 years
2. Symptomatic ischaemic heart disease or heart disease of other aetiology
3. Multiple cardiovascular risk factors, Prinzmetal angina
4. Raynaud's phenomenon
5. Diseases that influence metabolism or excretion of sumatriptan
6. Severe, acute mountain sickness with ataxia, focal neurological symptoms, or changes in mental status
7. Pregnancy or nursing women
8. Known intolerance to sumatriptan
9. Abuse of opioids or ergotamine analgesics
10. Abuse of alcohol or intake of > 15 grams of ethanol in the past 24 h
11. Co-medication with serotonin-interferent drugs
12. Intake of analgesics 4 h or ergotamine 24 h preceding the study
13. Acetazolamide, corticosteroid, or nifedipine medication

Interventions	**Intervention group (n = 14)** 1. Name: sumatriptan; route: oral; dose: 100 mg; frequency: every 3 h; duration of the intervention: not clearly reported 2. Control group (n = 15): placebo 100 mg; route: oral; dose: 100 mg; frequency and duration not clearly reported **Co-intervention** 1. Paracetamol (500 mg) if headache pain was not relieved 3 h after administration of the study drug. Quote: "When headache had improved within 1 hours after administration of the study drug but recurred after 3 hours, an oral dose of 100 mg of sumatriptan was given" (page 389)
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Improvement of high altitude headache ("defined as reduction of the headache score by 1 point"). Assessed at 1 h, 3 h, and 12 h after medication 2. Lake Louise AMS score (LL score) 3. Blood pressure 4. Heart rate **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Italy, Capanna "Regina Margherita" in the Alps Valais **Altitude setting**: 4559 m (barometric pressure 430 mmHg to 440 mmHg) **Identifier number**: not reported **Study dates**: not reported **A priori sample estimation**: no **Conflicts of interest**: not reported **Funding/Support**: the Sezione Varallo del Club Alpino Italiano and of the Glaxo-Wellcome Company. Study drug was supplied by Glaxo-Wellcome company (Bad Oldesole, Germany)
Risk of bias	

Utiger 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization, without stratification, was performed in blocks of 4 subjects." Page 389
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgment of 'Low risk' or High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...sumatriptan and placebo had identical appearance..." Page 389
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about blinding of outcome assessment to permit judgment of 'Low risk' or High risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome data was not available in: 1. Sumatriptan group: 4 out of 14 (29%) participants 2. Placebo group: 5 out of 15 (33%) participants Reason: 1. severe acute mountain sickness (intense headache, vomiting, ataxia, or clouded consciousness) 2. acute illness of the examiner
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available
Other bias	High risk	Baseline differences: Quote: # 1: "despite strict randomisation in blocks of 4 subjects, all 6 women participating in the study were assigned to the placebo group, resulting in a significant difference of gender distribution between treatment groups" Page 389 Quote: # 2: "subjects of the sumatriptan group were somewhat older (mean age 38 versus 31 yr),..." Page 389 There was no statement considering the independence of authors with respect to those providing funding (source of industry bias)

Wang 1998

Methods	**Three-group parallel RCT, 1 centre** **ITT**: yes **Overall study quality**: high risk of bias **Unit of randomization**: participants **Follow-up period**: not clearly reported, apparently until recovery **Diagnosis of AMS** 1. Not reported **Scale used for assessing Acute Mountain Sickness**

Wang 1998 *(Continued)*

1. None

Participants	**Number of participants randomized**: 65 soldiers and railway workers **Sex**: men = 65 (100%) **Age**: mean 25 years **Baseline data** Symptom duration before recruitment: nifedipine: 9 days ± 3; nitric oxide: 8 days ± 3; conventional therapy: 8 days ± 3 **Inclusion criteria** 1. Patients diagnosed with high altitude pulmonary oedema. No additional inclusion criteria were applied **Exclusion criteria** 1. Not reported
Interventions	**Intervention group 1 (n = 24)** Name: nifedipine in addition to conventional therapy; nifedipine route: oral; dose: set at 20 mg at the first time, then 10 mg; frequency: every 8 h; duration of the intervention: until fully recovered **Intervention group 2 (n = 22)** Nitric oxide In addition to oral nifedipine. Nitric oxide (BG-951, co-developed by Guangzhou General Hospital and Beijing Factory of Analytical Machinery): dose: 10 ppm; route: inhalation, balanced with oxygen at 80% concentration level, inhalation rate was set at 8 L/min to 10 L/min; frequency and duration of the intervention: during 30 min **Control group (n = 19)** Conventional therapy: oxygen, intravenous furosemide, aminophylline and dexamethasone. Dose: not reported; route: inhalation in the case of oxygen; intravenous injection for furosemide, aminophylline and dexamethasone; frequency and duration: not reported **Co-intervention** 1. Penicillin, streptomycin were also used to prevent bacteria infection (mode of delivery: intramuscular injection)
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Disease course (duration of symptoms) 2. Time until pulmonary rales disappear 3. Time until shadows on chest radiograph disappear **Outcomes of interest in the review**: none
Notes	**Country**: China (military hospital at Kunlun Mountain at Sinkiang province) **Altitude setting**: 3700 m **Identifier number**: not reported **Study dates**: not reported **A priori sample estimation**: no **Conflicts of interest**: not reported

Wang 1998 *(Continued)*

Funding/Support: Military Medical and Health Research Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: “65 participants were randomised into 3 groups” Page 212, without specifying how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants In the Results section, authors summarized, “All of the 65 participants were fully recovered”. Comment: outcome data were available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Protocol not available
Other bias	Low risk	No other sources of bias identified

Wright 1994

Methods

***Results presented here correspond to the second of three experiments carried out by the researchers**

Experiment 1

1. Corresponds to an expedition 1 "a preliminary experiment comparing the effect of acetazolamide with methazolamide on blood gases was done in ten subjects" (acute mountain sickness was not an inclusion criteria)

Experiment 2

1. Corresponds to an expedition 2 "A placebo-controlled trial of acetazolamide for AMS was done in 13 subjects"

Experiment 3

1. Corresponds to an expedition 3 "randomised double blind comparison of methazolamide and dexamethasone. Data from the dexamethasone arm of the trial were insufficient and have been omitted"

Two-group parallel RCT, 1 centre

ITT: yes
Overall study quality: high risk of bias

Wright 1994 *(Continued)*

	Unit of randomization: participants **Follow-up period**: five days **Diagnosis of AMS** 1. "Headache, anorexia/nausea and insomnia were scored; 1 = mild, 2 = moderate and 3 = severe. A score of 3 was given for any degree of ataxia, confusion or disorientation. For entry into the acute therapy trial on these expeditions, a persistent AMS score of 3 determined at clinical interview was required" **Scale used for assessing Acute Mountain Sickness** 1. Self administered questionnaire of 18 questions (0: not present, 5: extreme) and a maximum score of 180
Participants	**Number of participants randomized**: 13 **Sex**: not reported for experiment 2 **Age**: not reported for experiment 2. They reported subjects aged 22 to 58 for the three experiments (see methods above) **Baseline data** 1. Self-administered AMS questionnaires 2. Placebo: 21.6 (+/- 11) 3. Acetazolamide: 33.3 (+/- 13.7) **Inclusion criteria** 1. Healthy; non obese; unacclimatized subjects; persistent AMS score of 3 **Exclusion criteria** 1. Not reported
Interventions	**Intervention group (n = 6)** 1. Acetazolamide; route: oral; dose: 20 mg Kg^{-1} (1 to 1.5 grams) initially and then 500 mg daily **Control group (n = 7)** 1. Placebo: "all drugs and placebo were prepared in identical gelatin capsules" **Co-intervention** 1. None reported
Outcomes	**Not pre-fixed as 'primary' or 'secondary'** 1. Headache worsening (proportion of participants per group) 2. Response to acute therapy: using self-administered AMS questionnaires of 18 questions scored 0 (not present) to 5 (extreme) (mean, SD and proportion with improvement) 3. Blood gases 4. Cerebral blood flow after allocation, before the administration of study drug and 20 h to 24 h later **Outcomes of interest in the review** 1. Reduction in illness severity scores of AMS
Notes	**Country**: Karakoram mountains, located in the borders between Pakistan, India and China **Altitude setting**: 3200 to 5486 m

Wright 1994 *(Continued)*

Identifier number: not reported

Study dates: not reported

A priori sample estimation: no

Conflicts of Interest: not reported

Funding/Support

1. "The work was supported by grants from the Arthur Thomson and the Wellcome Trusts." "Lederle Laboratories UK kindly supplied the acetazolamide"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "subjects were randomly allocated on a double-blind basis" Page 51
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote: "subjects were randomly allocated on a double-blind basis" Page 51
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "all drugs and placebo were prepared in identical gelatin capsules" Page 51 However, blinding was discontinued "Six of the placebo group were given 1.5 grams oral acetazolamide 24 hours after entry into the trial because AMS symptoms had persisted. At this point all subjects were aware of their treatment status" Page 51
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "all drugs and placebo were prepared in identical gelatin capsules" Page 51 However, blinding was discontinued "Six of the placebo group were given 1.5 grams oral acetazolamide 24 hours after entry into the trial because AMS symptoms had persisted. At this point all subjects were aware of their treatment status" Page 51
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes: no withdrawals. Outcome data was available for all participants
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. Protocol not available
Other bias	High risk	Some participants in experiment 2 could have participated in the other two experiments (see methods above). Quote: "23 were studied during one of the three expeditions, six in two expeditions and three subjects in all three expeditions." Page 50. There is not enough information regarding how many participants from the second expedition were involved in the other two, and how much time passed between one expedition and another to identify a carry-over effect. There was no statement considering the independence of authors with respect to those providing funding (source of industry bias)

List of acronyms and abbreviations used in these tables

RCT: randomized controlled trial; **ITT**: intention-to-treat analysis; **AMS**: acute mountain sickness; **AMS-C**: acute mountain sickness-cerebral; **h**: hour(s); **HACE**: high altitude cerebral oedema; **HAH**: high altitude headache; **HAPE**: high altitude pulmonary oedema; **LL**: Lake Louise; **mbar**: millibar (millibars, a derived unit of the metric unit of pressure bars); **MCA**: median cerebral artery; **min**: minute; **mmol**: millimoles; **n**: number; **NSAID**: nonsteroidal anti-inflammatory drugs; **SD**: standard deviation; **VAS**: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anand 1998	Cross-over trial. The study design was considered inappropriate to the review question
Bates 2007	It is not a randomized trial
Benedetti 2015	Study intervention used for the prevention of HAI
Bradwell 1988	It is not a randomized trial
Broome 1994	Cross-over trial. The study design was considered inappropriate to the review question: outcomes were reported after the patients received both intervention and control treatment
Brown 1977	Study intervention used for the prevention of HAI
Burtscher 1995	Cross-over trial. The study design was considered inappropriate to the review question.
Bärtsch 1992	Narrative review
Bärtsch 1994	It is not a randomized trial
Deshwal 2012	It is not a randomized trial
Fagenholz 2007	It is a case series study
Forster 1982	Study intervention used for the prevention of HAI
Forwand 1968	Study intervention used for the prevention of HAI
Levine 1989	Cross-over trial. The study design was considered inappropriate to the review question: outcomes were reported after the patients received both intervention and control treatment
Li 2010	Quasi-randomized study (randomization was based on the participants' hospitalization registration number)
Maggiorini 1995	Narrative review
Meehan 1986	The study population were healthy male volunteers
Oelz 1989	It is not a randomized trial
Oelz 1992	It is not a randomized trial
Roggla 2001	Study intervention used for studying AMS pathophysiology
Wright 1988	We wrote to info@bmres.co.uk in 2014 in order to contact the main author: Dr Wright (a.wright@bmres.org.uk) replied saying that the study was not randomized
Yan 2010	Quasi-randomized study (randomization was based on the participants' hospitalization registration number)

Study	Reason for exclusion
Yanamandra 2016	Quasi-randomized study (randomization was based on the participants' first name's starting initial)
Zhang 2012	The study Intervention does not meet the review eligibility criteria (Bundle treatment)

Acronyms and abbreviations used in these tables
AMS: acute mountain sickness; HAI: high altitude illness

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-TRC-13003298

Trial name or title	Oral trimetazidine for reducing the symptoms of acute mountain sickness and improving exercise performance
Methods	Single centre randomized, parallel, double-blind, controlled, prospective trial
Participants	Shapingba District and Tibetan Autonomous Prefecture of Garzê (Chongqing, and Sichuan), China **Inclusion criteria** 1. Aged between 18 and 35 years, including 18 and 35 years 2. People acutely ascending to high altitude. The gender ratio depends on actual situation 3. There is no history of plateau for a long time exposure 4. Before assessment, all subjects must be voluntary and sign a written informed consent **Exclusion criteria** 1. The recent history of taking acute mountain sickness prevention drugs 2. Engaged in specialized sports training 3. Subjects with bad compliance 4. The recent history of upper respiratory tract infection 5. Subjects cannot take the drugs in our trial because of allergic history or other reasons 6. Subjects with psychological or neurological disorder, and other conditions which are not appropriate for our trial
Interventions	**Interventions** 1. Oral trimetazidine, 20 mg three times a day (20 participants) **Control** 1. Oral placebo, the same dosage as oral trimetazidine (20 participants)
Outcomes	Lake Louise Score
Starting date	According to the Chinese Clinical Trial Registry, the study is currently recruiting (last update February 2016); however the reported study completion time is from 30 June 2013 to 30 December 2013
Contact information	Qin Jun; Huang Lan qinjunxq@126.com; huanglan260@yahoo.com.cn
Notes	Approved by ethic committee: yes. Institute of Cardiovascular Diseases of PLA, Xinqiao Hospital, Third Military Medical University, Chongqing, China Primary sponsor: Institute of Cardiovascular Diseases of PLA, Xinqiao Hospital, Third Military Medical University, Chongqing, China

ChiCTR-TRC-13003298 *(Continued)*

	We have contacted the study leader, and the applicant by e-mail in order to obtain more information (February 2017); answer is pending.

NCT01522326

Trial name or title	Comparison of metoclopramide and ibuprofen for the treatment of acute mountain sickness
Methods	**Allocation**: randomized **Endpoint classification**: efficacy study **Intervention model**: parallel assignment **Primary purpose**: treatment **Masking**: double blind (subject, caregiver, investigator)
Participants	Trekkers travelling through the Annapurna Circuit in Nepal during the 3-month time period of March to May 2012 Acute mountain sickness/high altitude headache **Age group**: adult/senior **Sex**: male and female **Enrolment**: 300 **Inclusion criteria** 1. Presence at Manang recruitment centre (at approximately 11,500 ft) during the dates March through May 2012. 2. Recent increase in altitude of >1000 ft vertical in last 24 h 3. Presence of headache and at least one other symptom required for diagnosis of acute mountain sickness (including nausea, vomiting, fatigue, weakness, dizziness, lightheadedness or poor sleeping) **Exclusion criteria** 1. Age less than 19 years old 2. Known allergy or contraindication to either ibuprofen or metoclopramide 3. Evidence of severe high altitude illness (e.g. High altitude pulmonary oedema (HAPE) as evidenced by dyspnoea at rest; or of High altitude cerebral oedema (HACE) as evidenced by altered mental status or ataxia) 4. Known or suspected pregnancy 5. Use of other analgesic or antiemetic within 8 h of study enrolment 6. History of migraines or other chronic headache disorders 7. Inability to provide informed consent
Interventions	**Drug: ibuprofen** 1. "150 subjects with acute mountain sickness will be randomly assigned to take ibuprofen"; "Ibuprofen 400 mg tablet. Take one dose by mouth" **Drug: metoclopramide** 1. "150 subjects with acute mountain sickness will be randomly assigned to take metoclopramide"; "Metoclopramide 10 mg tablet. Take one tablet by mouth"

NCT01522326 *(Continued)*

Outcomes	**Headache and nausea (visual analogue scales)** 1. Quote: "subjects will complete 100 mm visual analogue scales of both headache and nausea at time zero, 30, 60, and 120 minutes after taking the study medication. Visual analogue scales are a valid assessment of symptom severity for acute mountain sickness" **Lake Louise acute mountain sickness Score** 1. Quote: "subjects will take the Lake Louise Acute Mountains Sickness score before taking the medication and 120 minutes after taking the medication. The Lake Louise Acute Mountain Sickness Score is a standard measure of the severity of acute mountain sickness and is commonly used in studies involving acute mountain sickness"
Starting date	March 2012 Currently recruiting, according to ClinicalTrials.gov registry (last verified February 2017) Estimated study completion date: March 2017
Contact information	John B Tanner, MD JBTANNER@PARTNERS.ORG Principal Investigator: Norman S Harris, MD, MFA Massachusetts General Hospital
Notes	International study **Sponsor/collaborators**: Massachusetts General Hospital **URL**: ClinicalTrials.gov/show/NCT01522326

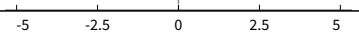
DATA AND ANALYSES

Comparison 1. Acetazolamide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AMS symptoms (standardized)	2	25	Std. Mean Difference (IV, Random, 95% CI)	-1.15 [-2.56, 0.27]

Analysis 1.1. Comparison 1 Acetazolamide versus placebo, Outcome 1 AMS symptoms (standardized).

Study or subgroup	Acetazolamide N	Acetazolamide Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Grissom 1992	6	1 (0.6)	6	2.5 (0.8)		44.15%	-1.96[-3.44,-0.48]
Wright 1994	6	23 (16.5)	7	30.8 (12.4)		55.85%	-0.5[-1.62,0.61]
Total ***	**12**		**13**			**100%**	**-1.15[-2.56,0.27]**
Heterogeneity: Tau^2=0.61; Chi^2=2.36, df=1(P=0.12); I^2=57.71%							
Test for overall effect: Z=1.59(P=0.11)							



APPENDICES

Appendix 1. Risk categories for acute high altitudes

Risk categories	Description
Luks 2010	
Low	Individuals with no prior history of altitude illness and ascending to ≤ 2800 m/ 9186 feet.
Low	Individuals taking ≥2 days to arrive at 2500 to 3000 m/ 8202 to 9842 feet with subsequent increases in sleeping elevation < 500m by day/ 1640 feet by day.
Moderate	Individuals with prior history of AMS and ascending to 2500 to 2800 m (8202 to 9186 feet) in one day.
Moderate	No history of AMS and ascending to > 2800 m (9186 feet) in one day.
Moderate	All individuals ascending > 500 m/d (1640 feet) (increase in sleeping elevation) at altitudes above 3000 m / 9842 feet.
High	History of AMS and ascending to ? 2800 m / 9186 feet in one day.
High	All individuals with a prior history of HAPE or HACE.
High	All individuals ascending to > 3500 m/ 11,482 feet in one day.
High	All individuals ascending >500 m/ 1640 feet /d increase in sleeping elevation above > 3500 m/ 11,482 feet.
High	Very rapid ascents (e.g., Mt. Kilimanjaro).

Appendix 2. Medical terms glossary

Term	Definition
Anorexia	The lack or loss of appetite accompanied by an aversion to food and the inability to eat
Ataxia	Impairment of the ability to perform smoothly coordinated voluntary movements
Brian herniation	Protrusion of tissue, structure, or part of an organ through the bone, muscular tissue, or the membrane by which it is normally contained
Dyspnoea	Difficult or laboured breathing
Dizziness	An imprecise term which may refer to a sense of spatial disorientation, motion of the environment, or lightheadedness
Endothelium	A layer of epithelium that lines the heart, blood vessels (endothelium vascular), lymph vessels (endothelium lymphatic), and the serous cavities of the body

(Continued)

Fatigue	The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli
Hallucination	Subjectively experienced sensations in the absence of an appropriate stimulus, but which are regarded by the individual as real
Headache	The symptom of pain in the cranial region
Hypoxia	A disorder characterized by a reduction of oxygen in the blood
Insomnia	Disorders characterized by impairment of the ability to initiate or maintain sleep
Lightheadedness	See dizziness
Nausea	An unpleasant sensation in the stomach usually accompanied by the urge to vomit
Pulmonary oedema	An unpleasant sensation in the stomach usually accompanied by the urge to vomit
Pulmonary alveoli	Small polyhedral outpouchings along the walls of the alveolar sacs, alveolar ducts and terminal bronchioles through the walls of which gas exchange between alveolar air and pulmonary capillary blood takes place
Seizures	Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells.Clinicalmanifestations include abnormal motor, sensory and psychic phenomena

Source: http://www.ncbi.nlm.nih.gov/mesh

Appendix 3. The most frequents adverse effects of the pharmacological interventions.

Drug	Description and contraindications	Adverse events
Paracetamol	It is a non-steroidal anti-inflammatory drug	Paracetamol may cause liver damage
Acetazolamide	Acetazolamide, an inhibitor of the enzyme carbonic anhydrase. Hypersensitivity to acetazolamide or any excipients in the formulation. Since acetazolamide is a sulfonamide derivative, cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible. Acetazolamide therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloraemic acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy	Adverse reactions, occurring most often early in therapy, include paraesthesias, particularly a “tingling” feeling in the extremities, hearing dysfunction or tinnitus, loss of appetite, taste alteration and gastrointestinal disturbances such as nausea, vomiting and diarrhoea; polyuria, and occasional instances of drowsiness and confusion
Aspirin	It is a non-steroidal anti-inflammatory drug.	Reye’s syndrome (a rare but serious illness). Stomach bleeding
Dexamethasone	Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body’s immune responses to diverse stimuli.	Several adverse events (e.g. hyperglycaemia, fluid retention, hypokalaemic alkalosis, potassium loss, sodium retention)

(Continued)

	Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems. Contraindicated in systemic fungal infections	
Furosemide	It is potent diuretic. Furosemide is contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide	The principal signs and symptoms of overdose with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalaemia and hypochloraemic alkalosis, and are extensions of its diuretic action
Gabapentin	Gabapentin is an anticonvulsant. Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients	Somnolence, dizziness, ataxia, fatigue, and nystagmus
Ibuprofen	It is a nonsteroidal anti-inflammatory drug (NSAID)	Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. It is a an NSAID, which may cause severe stomach bleeding
Magnesium	Magnesium should not be administered if there is renal impairment, marked myocardial disease or to comatose patients	The usual precautions for parenteral administration should be observed. Administer with caution if flushing and sweating occurs. Respiration and blood pressure should be carefully observed during and after administration of magnesium chloride injection
Medroxyprogesterone	It is a derivative of progesterone. Contraindications: known or suspected pregnancy or as a diagnostic test for pregnancy, undiagnosed vaginal bleeding, known or suspected malignancy of breast, active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease, liver dysfunction or disease, known sensitivity to medroxyprogesterone acetate	Fluid retention, and several others related with the prolonged use
Methazolamide	Methazolamide is a potent inhibitor of carbonic anhydrase. Methazolamide therapy is contraindicated in situations in which sodium and/or potassium serum levels are depressed, in cases of marked kidney or liver disease or dysfunction, in adrenal gland failure, and in hyperchloraemic acidosis. In patients with cirrhosis, use may precipitate the development of hepatic encephalopathy	Adverse reactions, occurring most often early in therapy, include paraesthesias, particularly a “tingling” feeling in the extremities; hearing dysfunction or tinnitus; fatigue; malaise; loss of appetite; taste alteration; gastrointestinal disturbances such as nausea, vomiting, and diarrhoea; polyuria; and occasional instances of drowsiness and confusion
Nifedipine	It is a calcium channel blocker. Nifedipine must not be used in cases of cardiogenic shock. It is contraindicated in patients with a known hypersensitivity to any component of the tablet	Headache, flushing/heat sensation, dizziness, fatigue/asthenia, nausea
Temazepam	It is a benzodiazepine hypnotic agent. It is contraindicated in women who are or may become pregnant	Drowsiness

(Continued)

Theophylline	Theophylline is classified as amethylxanthine. Theophylline should be used with extreme caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition: active peptic ulcer disease, seizure disorders and cardiac arrhythmias (not including bradyarrhythmias)	Nausea, vomiting, headache, and insomnia

Source: DailyMed. dailymed.nlm.nih.gov/dailymed/about.cfm

Appendix 4. Search strategy

Search strategy for CENTRAL, in the Cochrane Library

#1 MeSH descriptor Altitude Sickness explode all trees
#2 MeSH descriptor Pulmonary Edema explode all trees
#3 MeSH descriptor Altitude, this term only
#4 (illnes* or sicknes* or ((cerebral or pulmonary) and (oedema or edema)))
#5 altitude
#6 (#5 AND #4)
#7 (mountain near (sickness or illness)) or (AMS or HACE or HAPE or HAI):ti,ab
#8 (#1 OR #2 OR #3 OR #6 OR #7)
#9 (nifedipine or dexamethasone or theophylline or acetazolamide or medroxyprogesterone or aspirin or ibuprofen or acetaminophen or sumatriptan or gabapentin or furosemide or spironolactone or calcium channel blocker* or selective inhibitor* of phosphodiesterase type 5 or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase-inhibitor* or carbonic anhydrase inhibitor* or 5-HT1 receptor agonist*or N-methyl-D-aspartate antagonist* or oxygen or descent* or hyperbaric chamber or portable pressure bag* or Gamow bag* or breathing system* or positive airway pressure) or (therapy or treat*):ti,ab
#10 (#8 AND #9)

Search strategy for MEDLINE (Ovid SP)

1. exp Altitude Sickness/ or exp Pulmonary Edema/ or Altitude/ or (high-altitude adj5 (illnes*or sicknes* or ((cerebral or pulmonary) and (oedema or edema))))).mp. or (high altitude adj5 (illnes*or sicknes* or ((cerebral or pulmonary) and (oedema or edema))))).mp. or (highaltitude adj5 (illnes*or sicknes* or ((cerebral or pulmonary) and (oedema or edema))))).mp. or (mountain adj3 (sickness or illness)).af. or (AMS or HACE or HAPE or HAI).ti,ab.
2. (nifedipine or dexamethasone or theophylline or acetazolamide or medroxyprogesterone or aspirin or ibuprofen or acetaminophen or sumatriptan or gabapentin or furosemide or spironolactone or calcium channel blocker* or selective inhibitor* of phosphodiesterase type 5 or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase-inhibitor* or carbonic anhydrase inhibitor* or 5-HT1 receptor agonist*or N-methyl-D-aspartate antagonist* or oxygen or descent* or hyperbaric chamber or portable pressure bag* or Gamow bag* or breathing system* or positive airway pressure).mp. or (therapy or treat*).ti,ab
3. 1 and 2
4. ((randomised controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh
5. 3 and 4

Search strategy for Embase (www.embase.com)

1. 'altitude disease ' or altitude NEAR/3 (illnes* OR sicknes*) or mountain NEAR/3 (sickness or illness) or ((altitude or mountain) AND cerebral:ab,ti OR pulmonary:ab,ti OR lung:ab,ti AND (oedema:ab,ti OR edema:ab,ti)) or ams:ab,ti OR have:ab,ti OR hape:ab,ti OR hai:ab,ti

2. nifedipine or dexamethasone or theophylline or acetazolamide or medroxyprogesterone or aspirin or ibuprofen or acetaminophen or sumatriptan or gabapentin or furosemide or spironolactone or calcium channel blocker* or selective inhibitor* of phosphodiesterase type 5 or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase-inhibitor* or carbonic anhydrase inhibitor* or 5-HT1 receptor agonist*or N-methyl-D-aspartate antagonist* or oxygen or descent* or hyperbaric chamber or portable pressure bag* or Gamow bag* or breathing system* or positive airway pressure or (therapy or treat*):ab,ti
3. 1 and 2
4. placebo:ab,ti or 'controlled study':ab,ti or random*:ab,ti or trial*:ab,ti or ((singl* or doubl* or trebl* or tripl*) NEAR/3 (blind* or mask*))
5. 3 and 4

Search strategy for LILACS via BIREME interface

"EDEMA CEREBRAL" or "edema pulmonary$" or "mountain sickness" or "high-altitude sickness" or ?montaña enfermedad? or ?o mal da montanha? or ?doença de alta altitude? or ?mal de altura?

tw:("mountain sickness") OR ("high-altitude sickness") OR ("enfermedad de montaña") or ("mal da montanha") or ("doença de alta altitude") or mh:("Mal de Altura")

Search strategy for ISI Web of Science

#1 TS= ("high altitude" NEAR illnes*) or TS= ("high altitude" NEAR sicknes*) or TS= ("high altitude" NEAR "cerebral *edema") or TS= ("high altitude" NEAR "pulmonar* *edema") or TS=(mountain NEAR (sicknes* or illnes*)) or TS=(AMS or HACE or HAPE or HAI)
#2 TS=(nifedipine or dexamethasone or theophylline or acetazolamide or medroxyprogesterone or aspirin or ibuprofen or acetaminophen or sumatriptan or gabapentin or furosemide or spironolactone or calcium channel blocker* or selective inhibitor* of phosphodiesterase type 5 or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase-inhibitor* or carbonic anhydrase inhibitor* or 5-HT1 receptor agonist*or N-methyl-D-aspartate antagonist* or oxygen or descent* or hyperbaric chamber or portable pressure bag* or Gamow bag* or breathing system* or positive airway pressure) or TI=(therapy or treat*)
#3 #2 and #1
#4 TS=((random* or controlled or clinical or multicent* or prospective*) NEAR trial*) or TS=((single or double or triple or treble) NEAR trial*)
#5 #3 and #4

Search strategy for CINAHL (EBSCO host)

S1 ((MM "Altitude Sickness") OR (MH "Pulmonary Edema")) OR ((high?altitude and (illnes*or sicknes* or ((cerebral or pulmonary) and (oedema or edema))))) OR ((mountain and (sickness or illness)) or (AMS or HACE or HAPE or HAI))
S2 (nifedipine or dexamethasone or theophylline or acetazolamide or medroxyprogesterone or aspirin or ibuprofen or acetaminophen or sumatriptan or gabapentin or furosemide or spironolactone or calcium channel blocker* or selective inhibitor* of phosphodiesterase type 5 or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase-inhibitor* or carbonic anhydrase inhibitor* or 5-HT1 receptor agonist*or N-methyl-D-aspartate antagonist* or oxygen or descent* or hyperbaric chamber or portable pressure bag* or Gamow bag* or breathing system* or positive airway pressure) OR AB (prevent* or therapy or treat*)
S3 S1 and S2
S4 ((MM "Randomized Controlled Trials") OR (MM "Random Assignment") OR (MH "Clinical Trials") OR (MH "Multicenter Studies") OR (MH "Double-Blind Studies") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind Studies")) OR (random* or ((controlled or clinical) and trial*))
S5 S3 and S4

Search strategy for Wanfang (Wanfangdata.com)

"Acute Mountain Sickness" OR "High Altitude Pulmonary Edema" OR "High Altitude Cerebral Edema"

Also in Chinese (高山病、高原肺水肿、高原脑水肿)

Appendix 5. WHO International Trials Registry Portal search

Advanced search: Altitude Sickness OR Altitude illness OR acute mountain sickness OR High-altitude edema OR high-altitude oedema (in the title field)

Appendix 6. Data collection form

Notes on using a data extraction form:

· Be consistent in the order and style you use to describe the information for each report.

· Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.

Review title or ID
Interventions for Treating High Altitude Illness

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report ID *(if different to Study ID)*	**Report IDs of other reports of this study** *(e.g. duplicate publications, follow-up studies)*

Notes:

General Information

Date form completed *(dd/mm/yyyy)*
Name/ID of person extracting data
Reference citation
Study author contact details
Publication type *(e.g. full report, abstract, letter)*
Notes:

Study eligibility

Study Characteristics	**Eligibility criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Eligibility criteria met?**			**Location in text or source** *(pg & /fig/table/other)*
		Yes	No	Unclear	
Type of study	Randomized Controlled Trial				
Participants	Were they people with HAI (AMS/HACE and HAPE, or both).				
Types of intervention	Did one group receive A) Non-pharmacological interventions				

(Continued)

	1. Rest and oxygen 2. Descent 3. Hyperbaric chamber 4. Portable pressure bag or Gamow bag 5. Breathing system designed to conserve oxygen supplies at high altitude 6. Positive airway pressure B) Pharmacological interventions 1. Carbonic anhydrase inhibitors (e.g. acetazolamide) 2. Glucocorticosteroids: dexamethasone and medroxyprogesterone 3. Non-steroidal anti-inflammatory drugs (NSAIDs): ibuprofen, paracetamol and aspirin 4. Selective 5-hydroxytryptamine(1) receptor agonist: sumatriptan 5. Inhaled nitric oxide 6. Anticonvulsivant drugs (e.g. gabapentin) 7. Diuretics (e.g. frusemide) 8. Calcium channel blockers: nifedipine 9. Magnesium
Types of comparison	Did the comparison group receive a Placebo, monotherapy or any combination (non-pharmacological plus pharmacological; pharmacological interventions).
INCLUDE EXCLUDE	
Reason for exclusion	**DO NOT PROCEED IF STUDY IS EXCLUDED FROM REVIEW**
Notes:	

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	**Location in text or source** *(pg &/fig/table/other)*
Country *(where the study was conducted)*		
Design *(e.g. parallel, cluster)*		
Was the study multicentre? *(if yes, state No. of centres)*		
Funders of the trial		

(Continued)

Duration of trial *(state start date and end date of trial)*	
Duration of participation *(from start of recruitment to last follow-up)*	
Ethical approval needed/ obtained for study	Yes No Unclear
Notes:	

Participants

	Description *Include comparative information for each intervention or comparison group if available*	**Location in text or source** *(pg & /fig/table/other)*
Population description *(describe any risk factors, and criteria for diagnosing high-altitude pulmonary edema)*		
Setting *(from where were participants enrolled?)*		
Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants *(e.g. phone, mail, clinic patients)*		
Total no. randomized		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/Ethnicity		
Notes:		

Intervention groups

	Description as stated in report/paper	Location in text or source *(pg & /fig/table/other)*
Drug name		
No. randomized to group *(specify whether no. people or clusters)*		
Details of the drug/intervention *(e.g. brand, look, taste)*		
Dosing regimen *(e.g. dose, frequency, duration)*		
Mode of Delivery *(e.g. oral)*		
Co-interventions *(any additional interventions given)*		
Notes:		

Placebo Group

	Description as stated in report/paper	Location in text or source *(pg & /fig/table/other)*
Comparison name		
No. randomized to group *(specify whether no. people or clusters)*		
Details of placebo *(e.g. similarity to intervention)*		
Dosing regimen *(e.g. dose, frequency, duration)*		
Mode of Delivery *(e.g. oral)*		
Co-interventions *(any additional interventions given)*		
Notes:		

Outcomes

	Description as stated in report/paper	Location in text or source *(pg & /fig/table/other)*

(Continued)

Outcome name	**All-cause mortality:** • The number of deaths from any cause divided by the number of the participants in each group. • The number of deaths from HAPE or HACE divided by the number of participants in each group. To determine how many deaths were caused by HAPE or HACE. • The number of deaths by HAPE or HACE divided by the number of participants affected by HAPE or HACE in each group. To determine how lethal were HAPE or HACE.
Time points measured *(specify whether from start or end of intervention)*	
Time points reported	
Person measuring/ reporting	
How was pain assessed? *(measurement scale)*	
Scales: upper and lower limits *(indicate whether high or low score is good)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Notes:	

	Description as stated in report/paper	**Location in text or source** *(pg & /fig/table/other)*
Outcome name	**Complete relief of HAPE symptoms (in terms of course duration)**	
What adverse events were assessed?		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Person measuring/ reporting		

(Continued)

How were adverse events assessed? *(measurement scale, diaries, healthcare notes, participant recall)*	
Scales: upper and lower limits – if applicable *(indicate whether high or low score is good)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	Not reported
Notes:	

	Description as stated in report/paper	**Location in text or source** *(pg & /fig/table/other)*
Outcome name	**Reduction in illness severity scores of AMS (headache, nausea, insomnia and dizziness; alone or in any combination) evaluated by the Lake Louise Questionnaire, Environmental Symptoms Questionnaire or any other validated scale. Because these different scales are not directly comparable, we will analyse the results for each scale separately. Any pooled analysis will be carefully justified.**	
What adverse events were assessed?		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Person measuring/ reporting		
How were adverse events assessed? *(measurement scale, diaries, healthcare notes, participant recall)*		
Scales: upper and lower limits – if applicable *(indicate whether high or low score is good)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Notes:		

	Description as stated in report/paper	Location in text or source *(pg & /fig/table/other)*
Outcome name	**Adverse events:** • adverse events: total adverse events and total serious adverse events. Adverse events will be defined as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (Nebeker 2004). • adverse drug reaction will be defined as "a response to a drug which is noxious and uninitiated and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic functions" (Nebeker 2004).	
What adverse events were assessed?		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Person measuring/ reporting		
How were adverse events assessed? *(measurement scale, diaries, healthcare notes, participant recall)*		
Scales: upper and lower limits – if applicable *(indicate whether high or low score is good)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Notes:		

Data and analysis

Dichotomous/Continuous outcome:

	Description as stated in report/paper	Location in text or source *(pg & /fig/table/other)*

(Continued)

Comparison	
Outcome	
Subgroup	
Time point *(specify from start or end of intervention)*	
Results	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*	
No. missing participants	
Reasons missing	
No. participants moved from other group	
Reasons moved	
Unit of analysis *(by individuals, cluster/groups or body parts)*	
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify, e.g. correlation adjustment)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Risk of Bias assessment

Domain	**Risk of bias**			**Support for judgement** *(include direct quotes where available with explanatory comments)*	**Location in text or source** *(pg & /fig/table/other)*
	Low risk	High risk	Unclear		
Random sequence generation *(selection bias)*					
Allocation concealment *(selection bias)*					

(Continued)

Blinding of participants and personnel

*(performance bias)**Outcome group: HAPE symptoms and course duration***

Outcome group: Adverse events

Blinding of outcome assessment

(detection bias)

Outcome group: HAPE symptoms and course duration

Outcome group: Adverse events

Incomplete outcome data

(attrition bias)

Outcome group: HAPE symptoms and course duration (short term: 24hrs)

Outcome group: HAPE symptoms and course duration (long term: 2-7 days)

Outcome group: Adverse events

Selective outcome reporting?

(reporting bias)

Notes:

Other information

Correspondence required for further study information *(from whom, what and when)*

Any additional comments you would like to make about this study:

Definitions

Clusters	A group of participants who have been allocated to the same intervention arm together, as in a cluster-randomized trial, e.g. a whole family, town, school or patients in a clinic may be allocated to the same intervention rather than separately allocating each individual to different arms.
Co-morbidities	The presence of one or more diseases or conditions other than those of primary interest. In a study looking at treatment for one disease or condition, some of the individuals may have other diseases or conditions that could affect their outcomes.

(Continued)

Compliance	Participant behaviour that abides by the recommendations of a doctor, other health care provider or study investigator (also called adherence or concordance).
Exclusions	Participants who were excluded from the study or the analysis by the investigators.
Imputation	Assuming a reasonable value for a measure where the true value is not available (e.g. assuming last observation carried forward for missing participants).
Reanalysis	Additional analysis of a study's results by a review author (e.g. to introduce adjustment for correlation that was not done by the study authors).
Report ID	A unique ID code given to a publication or other report of a study by the review author (e.g. first author's name and year of publication). If a study has more than one report (e.g. multiple publications or additional unpublished data) a separate Report ID can be allocated to each to help review authors keep track of the source of extracted data.
Sociodemographics	Social and demographic information about a study or its participants, including economic and cultural information, location, age, gender, ethnicity, etc.
Study ID	A unique ID code given to an included or excluded study by the review author (e.g. first author's name and year of publication from the main report of the study). Although a study may have multiple reports or references, it should have one single Study ID to help review authors keep track of all the different sources of information for a study.
Unit of allocation	The unit allocated to an intervention arm. In most studies individual participants will be allocated, but in others it may be individual body parts (e.g. different teeth or joints may be allocated separately) or clusters of multiple people.
Unit of analysis	The unit used to calculate N in an analysis, and for which the result is reported. This may be the number of individual people, or the number of body parts or clusters of people in the study.
Unit of measurement	The unit in which an outcome is measured, e.g. height may be measured in cm or inches; depression may be measured using points on a particular scale.
Validated	A process to test and establish that a particular measurement tool or scale is a good measure of that outcome.
Withdrawals	Participants who voluntarily withdrew from participation in a study before the completion of outcome measurement.

Appendix 7. 'Summary of findings' tables 1 and 2. Optimal information size calculations (performed with STATA 15)

'Summary of findings' table number 1

Reduction in symptom score severity at 12 hours

Estimated sample sizes for a two-sample means test Satterthwaite's t test assuming unequal variances
Ho: m2 = m1 versus Ha: m2 ≠ m1
Study parameters:

(Continued)

alpha = 0.0500
power = 0.8000
delta = −0.6000
m1 = 3.1000
m2 = 2.5000
sd1 = 2.3000
sd2 = 2.0000
Estimated sample sizes:
N = 408
N per group = 204

Adverse effects during treatment

Estimated sample sizes for a two-sample proportions test Pearson's chi-squared test
Ho: p2 = p1 versus Ha: p2 ≠ p1
Study parameters:
alpha = 0.0500
power = 0.8000
delta = 0.0010 (difference)
p1 = 0.0010
p2 = 0.0020
Estimated sample sizes:
N = 47,022
N per group = 23,511

'Summary of findings' table number 2

Reduction in symptom score severity

Gabapentin versus placebo

Estimated sample sizes for a two-sample means test Satterthwaite's t test assuming unequal variances
Ho: m2 = m1 versus Ha: m2 ≠ m1
Study parameters:
alpha = 0.0500
power = 0.8000
delta = -1.8300
m1 = 4.7500
m2 = 2.9200
sd1 = 3.1100
sd2 = 2.9100
Estimated sample sizes:
N = 88
N per group = 44

Magnesium versus placebo

Estimated sample sizes for a two-sample means test Satterthwaite's t test assuming unequal variances
Ho: m2 = m1 versus Ha: m2 ≠ m1
Study parameters:
alpha = 0.0500
power = 0.8000
delta = -1.3000
m1 = 10.3000
m2 = 9.0000
sd1 = 2.8000
sd2 = 3.5000

(Continued)

Estimated sample sizes:
N = 190
N per group = 95

Adverse effects

Acetazolamide versus placebo

Estimated sample sizes for a two-sample proportions test
Pearson's chi-squared test
Ho: p2 = p1 versus Ha: p2 ≠ p1
Study parameters:
alpha = 0.0500
power = 0.8000
delta = 0.0010 (difference)
p1 = 0.0010
p2 = 0.0020
Estimated sample sizes:
N = 47,022
N per group = 23,511

Appendix 8. Scores used in the included studies to measure symptoms and signs in acute mountain illness patients

Lake Louise Score (0 to 16) Roach 1993	
Headache	No headache (0)
	Mild headache (1)
	Moderate headache (2)
	Severe headache (3)
Gastrointestinal symptoms	None (0)
	Poor appetite or nausea (1)
	Moderate nausea &/or vomiting (2)

(Continued)

	Severe nausea &/or vomiting (3)
Fatigue &/or weakness	Not tired or weak (0) Mild fatigue/ weakness (1) Moderate fatigue/ weakness (2) Severe fatigue/ weakness (3)
Dizziness/lightheadedness	Not dizzy (0) Mild dizziness (1) Moderate dizziness (2) Severe dizziness, incapacitating (3)

Enviromental Symptoms Questionnaire	Used in Sampson 1983
1. I felt lightheaded	0-1-2-3-4-5
2. I had a headache	0-1-2-3-4-5
3. I felt sinus pressure	0-1-2-3-4-5
4. I felt dizzy	0-1-2-3-4-5
5. I felt faint	0-1-2-3-4-5
6. My vision was dim	0-1-2-3-4-5
7. My coordination was off	0-1-2-3-4-5
8. I was short of breath	0-1-2-3-4-5
9. It was hard to breathe	0-1-2-3-4-5
10.It hurt to breathe	0-1-2-3-4-5
11.My heart was beating fast	0-1-2-3-4-5
12.My heart was pounding	0-1-2-3-4-5
13.I had a chest pain	0-1-2-3-4-5
14.I had chest pressure	0-1-2-3-4-5
15.My hands were shaking/trembling	0-1-2-3-4-5
16.I had a muscle cramp	0-1-2-3-4-5
17.I had stomach cramps	0-1-2-3-4-5
18.My muscles felt tight or stiff	0-1-2-3-4-5
19.I felt weak	0-1-2-3-4-5
20.My legs or feet ached	0-1-2-3-4-5
21.My hands/arms/shoulders ached	0-1-2-3-4-5
22.My back ached	0-1-2-3-4-5
23.I had a stomachache	0-1-2-3-4-5
24.I felt sick to my stomach(nauseous)	0-1-2-3-4-5
25.I had gas pressure	0-1-2-3-4-5
26.I had diarrhoea	0-1-2-3-4-5
27.I felt constipated	0-1-2-3-4-5
28.I had to urinate more than usual	0-1-2-3-4-5
29.I had to urinate less than usual	0-1-2-3-4-5
30.I felt warn	0-1-2-3-4-5
31.I felt feverish	0-1-2-3-4-5
32.My feet were sweaty	0-1-2-3-4-5
33.I was sweating all over	0-1-2-3-4-5

(Continued)

34.My hands were cold	0-1-2-3-4-5
35.My feet were cold	0-1-2-3-4-5
36.I felt chilly	0-1-2-3-4-5
37.I was shivering	0-1-2-3-4-5
38.Parts of my body felt numb	0-1-2-3-4-5
39.My skin was burning or itchy	0-1-2-3-4-5
40.My eyes felt irritated	0-1-2-3-4-5
41.My vision was blurry	0-1-2-3-4-5
42.My ears felt blocked up	0-1-2-3-4-5
43.My ears ached	0-1-2-3-4-5
44.I couldn't hear well	0-1-2-3-4-5
45.My ears were ringing	0-1-2-3-4-5
46.My nose felt stuffed up	0-1-2-3-4-5
47.I had a runny nose	0-1-2-3-4-5
48.I had a nose bleed	0-1-2-3-4-5
49.My mouth was dry	0-1-2-3-4-5
50.My throat was sore	0-1-2-3-4-5
51.I was coughing	0-1-2-3-4-5
52.I lost my appetite	0-1-2-3-4-5
53.I felt sick	0-1-2-3-4-5
54.I felt hangover	0-1-2-3-4-5
55.I was thirsty	0-1-2-3-4-5
56.I felt tired	0-1-2-3-4-5
57.I felt sleepy	0-1-2-3-4-5
58.I felt wide awake (couldn't sleep)	0-1-2-3-4-5
59.My concentration was off .	0-1-2-3-4-5
60.I was more forgetful than usual	0-1-2-3-4-5
61.I felt worried or nervous	0-1-2-3-4-5
62.I felt irritable	0-1-2-3-4-5
63.I felt restless	0-1-2-3-4-5
64.Was bored	0-1-2-3-4-5
65.I felt depressed	0-1-2-3-4-5
66.I felt alert	0-1-2-3-4-5
67.Felt good	0-1-2-3-4-5
68.I was hungry	0-1-2-3-4-5

(Continued)

	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5
	0-1-2-3-4-5

Clinical Score: used in Bärtsch 1990 and Bärtsch 1993

"a score of 1 point each was given for headache, nausea, dizziness, insomnia, and facial oedema and 2 points each for headache resistant to mild analgesics taken within the previous 12 hours, nausea with vomiting, and ataxia documented by abnormal heel-to-toe walking or Romberg test."

Acute Muntain Syndrome Questionnaire used in Grissom 1992

Headache: transient or relieved with analgesic (1), severe or not relieved with analgesics (2)
Insomnia: difficulty falling asleep, frequent waking (1)
Dizziness (1)
Ataxia: difficulty in maintaining balance (1), steps off line (2), falls to ground or cannot finish test (3)
Severe lassitude: requires assistance for tasks of daily living (3)
Anorexia or nausea: true anorexia, not a distaste for diet (1)
Vomiting (1)
Dyspnoea on exertion: dyspnoea forces frequent halts, with slow recovery (2)
Dyspnoea at rest: marked dyspnoea at rest (3)

Clinical assessment used in Keller 1995

Change in mental state

1. Lethargy/lassitude
2. Disoriented/confused
3. Stupor/semiconscious

(Continued)

4. Coma

Ataxia (heel to toe walking)

1. Balancing manoeuvres
2. Steps off line
3. Falls down
4. Can't stand

Peripheral oedema

1. One location
2. Two or more locations

WHAT'S NEW

Date	Event	Description
20 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 1, 2012
Review first published: Issue 6, 2018

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Sign-off Editor

CONTRIBUTIONS OF AUTHORS

Daniel Simancas-Racines (DSR), Dimelza Osorio (DO), Juan VA Franco (JVAF), Ingrid Arevalo-Rodriguez (IAR), Yihan Xu (YX), Ricardo Hidalgo (RH), Arturo Martí Carvajal (AMC) (see Acknowledgements).

Conceiving the review: DSR and AMC

Designing the review: DSR and AMC

Co-ordinating the review: DO

Screening search results: DS, DO

Organizing retrieval of papers: DO

Screening retrieved papers against inclusion criteria: DSR, DO, IAR, YX

Appraising quality of papers: DSR, DO, JVAF, IAR, YX

Abstracting data from papers: DSR, DO, JVAF, IAR, YX

Writing to authors of papers for additional information: DO, JVAF

Obtaining and screening data on unpublished studies: DSR, DO

Data management for the review: DO, JVAF

Entering data into Review Manager 5 (RevMan 5): DSR, DO, JVAF

RevMan 5 statistical data: DSR, DO, JVAF

Other statistical analysis not using RevMan 5: none

Double entry of data: DSR, DO, JVAF

Interpretation of data: DSR, DO, JVAF, IAR, YX

Statistical inferences: DSR, DO, JVAF, IAR, YX

Writing the review: DSR, DO, JVAF, IAR, YX, RH

Providing guidance on the review: DSR, DO, JVAF, IAR, RH

Securing funding for the review: DSR, IAR, RH

Performing previous work that was the foundation of the present study: Arturo Martí-Carvajal, Alejandro G Gonzalez Garay

Guarantor for the review (one author): DSR

Persons responsible for reading and checking review before submission: DSR, DO, JVAF, IAR, YX

DECLARATIONS OF INTEREST

Daniel Simancas-Racines: no conflict of interest.

Dimelza Osorio: no conflict of interest.

Juan VA Franco: no conflict of interest.

Ingrid Arevalo-Rodriguez: no conflict of interest.

Yihan Xu: no conflict of interest.

Ricardo Hidalgo: no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador.

  Academic

External sources

- Iberoamerican Cochrane Center, Spain.

  Academic.
- Cochrane Anaesthesia, Critical and Emergency Care Group, Denmark.

  Academic

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the protocol (Martí-Carvajal 2012).

a. The list of authors has changed since the protocol was published. Martí-Carvajal AJ is not present and Franco VJA, Arevalo-Rodriguez I and Xu Y were included.
b. The background has been modified: some text related to the history of the concept of HAI has been deleted; and more recent references have been included. We also provided more details on how the interventions might work.
c. In the section Types of studies: in the protocol it was mentioned that "we will exclude quasi-randomized studies and prospective observational studies for evaluating clinical effectiveness. However, we will consider these studies for reports on adverse events".

We did not include quasi-randomized studies and prospective observational studies for reports on adverse events because the methodology to do this was not detailed in the protocol. However, we collected and analysed all information regarding adverse events from included studies.

d. In the section Types of interventions: in the protocol "frusemide" is listed as an intervention, which is the previous chemical denomination of the loop diuretic. Since the current denomination of this intervention is "furosemide" (Pubchem - Furosemide 2017), we used this denomination throughout the review.
e. In the section Types of outcome measures: we have included the definition of the outcome 'Complete relief of acute mountain sickness symptoms' by adding the following text: "defined as the complete absence of the acute mountain sickness symptoms by the end of the study".
f. This outcome was considered as a binary outcome as it was originally stated in the protocol at the section Measures of treatment effect.
g. In the section Electronic searches: the Chinese database Wanfang (Wanfangdata.com) was included in the search. This decision was taken by the review authors since several studies taking place in the Tibet and other areas of Asia may not appear in CENTRAL, MEDLINE, Embase, LILACS, ISI Web of Science and CINAHL.
h. In the section Searching other resources: we added the date of search of the World Health Organization International Clinical Trials Registry Platform (ICTRP; search date 24 February 2017) and of the principal investigators (3 March 2017). We added the following text after the dates: "Unpublished trials will be considered in updating of this review".
i. In the section Measures of treatment effect: the phrases "The unit of analysis will be the patient" and "We will collect and analyse a single measurement for each outcome from each participant" included in the protocol in the section of Measures of treatment effect were moved to the section Unit of analysis issues. We have considered adverse events (stated in the outcomes) as a synonym of safety. We have rewritten this section including the word 'safety' in brackets next to the words 'adverse events' that is the outcome defined for the review.
j. For analysis of continuous outcomes, we used standardized mean differences instead of mean differences, taking into account that included studies used different scales to measure the improvement of HAI symptoms. This analysis was used to present the findings about reduction in illness severity for acetazolamide versus placebo.
k. In the sections Summary of findings for the main comparison and Summary of findings 2 and GRADE: we have considered adverse events (stated in the outcomes) as a synonym of safety. We have rewritten this section including the word 'safety' in brackets next to the words 'adverse events' that is the outcome defined for the review. We also expanded the description on how we developed the 'Summary of findings' tables, and on how we took them into account to appraise the overall quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the outcomes we considered.
l. In Appendix 5: the search strategy in the WHO International Trials Registry Portal has been modified in order to improve sensitivity. Before: advanced search: high-altitude pulmonary oedema (in the title field). After: altitude Sickness OR Altitude illness OR acute mountain sickness OR High-altitude oedema OR high-altitude oedema (in the title field).
m. Due to scarcity of evidence we were unable to carry out the following methods:
    i. we planned to present the results of continuous outcomes as summary standardized mean difference with 95% CI. Instead, we presented the standardized mean difference for pooled results and the mean difference for individual studies.
    ii. exploration of heterogeneity and sensitivity analyses.
    iii. assessment of reporting biases.
    iv. use of fixed-effect and random-effects models.
    v. subgroup analysis

INDEX TERMS

Medical Subject Headings (MeSH)

Acetazolamide [therapeutic use]; Acute Disease; Altitude Sickness [*therapy]; Amines [therapeutic use]; Anticonvulsants [therapeutic use]; Atmospheric Pressure; Cyclohexanecarboxylic Acids [therapeutic use]; Dexamethasone [therapeutic use]; Gabapentin; Glucocorticoids [therapeutic use]; Hypertension, Pulmonary [therapy]; Magnesium [therapeutic use]; Randomized Controlled Trials as Topic; gamma-Aminobutyric Acid [therapeutic use]

MeSH check words

Adolescent; Adult; Humans